BEHAVIORAL AND NEURAL ASPECTS OF THE VESTIBULAR INFLUENCE ON BODILY SELF CONSCIOUSNESS

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ZUSAMMENFASSUNG

Man nimmt an, dass der Besitz eines Körpers die wichtigste Grundlage für das Erleben eines Selbst' darstellt. Mittlerweile gilt es auch als erwiesen, dass ein solches kohärentes körperliches Selbst, durch eine andauerende Integration körperbezogener sensorischer Reize repräsentiert wird. Generell wird ein kohärentes körperliches Selbst als Selbstverständlichkeit empfunden. In Wirklichkeit ist es aber ein sensibles Konstrukt. Insbesondere gewisse psychiatrische und neurologische Störungen zeigen auf, wie leicht das körperliche Selbstbewusstsein manipuliert werden kann. Um diese Störungsanfälligkeit auch bei gesunden Menschen zu demonstrieren, wird oftmals die Kongruenz multisensorischer Eindrücke so beeinflusst, dass körperliche Illusionen entstehen.

Obwohl es einige Inidizien dafür gibt, dass gerade das vestibuläre Organ in multisensorischen Prozessen essentiell für globale Aspekte des körperlichen Selbstbewusstsein ist, gibt es wenige Studien, welche diese Hypothese experimentell überprüft haben. Daher wurde in der ersten Studie untersucht, wie sich visuo-vestibuläre Konflikte auf das körperliche Selbsterleben auswirken. Während sich die subjektive Einschätzungen der Probanden als nicht aufschlussreich erwiesen haben, deuteten physiologische Veränderungen auf eine stärkere Identifikation mit einem fremden Körper hin.

In einer zweiten Studie wurde untersucht, wie Menschen mit einer speziellen Störung des Körperbewusstseins implizit vollständige und amputierte Körper wahrnehmen. Hierbei wurde gezeigt, dass Menschen mit der Störung im Gegensatz zu amputierten und nicht amputierten Menschen eher unvollständige Körper präferieren. Dieses Ergebnis zeigt vor allem auf, dass vereinfachte Modelle des körperlichen Selbstbewusstsein gerade bei komplexen Störungen, nicht in der Lage sind, deren Ursachen ausreichend zu erklären.

Ein weiterer wichtiger Punkt der körperlichen Selbstwahrnehmung kann ausserdem in der Schmerzverarbeitung ausgemacht werden. Deshalb wurde in einer dritten Studie untersucht, ob natürliche vestibuläre Stimulation eine schmerzstillende Wirkung hat, da im Vorfeld bereits gezeigt wurde, dass künstliche vestibuläre Stimulation einen Einfluss auf die Schmerzverarbeitung hat. In unserem Experiment hat sich gezeigt, dass sowohl natürliche vestibuläre Stimulation aber auch Kontrollbedingungen die Schmerzschwelle erhöht haben.

Insgesamt tragen die Ergebnisse der Studien zu einem besseren Verständnis vestibulärer Einflüsse auf die Körperwahrnehmung, im Speziellen das körperliche Selbst, bei.

SUMMARY

It has been hypothesized, that the experience of having a body is the key aspect for self consciousness and it has been recognized that such a coherent bodily self relies on ongoing multisensory integration of bodily sensory inputs. A coherent bodily self is mostly taken for granted, despite being highly influencable. In particular certain psychiatric and neurologic disorders demonstrate the malleabilty of bodily self consciousness. To induce comparable bodily illusions in healthy participants, experimental paradigms have been developed that mostly rely on visuo-tactile conflicts.

Although the involvement of the vestibular system in multisensory integration is supposed to be crucial for global aspects of bodily self consciousness, only few studies tested this hypothesis experimentally. Thus, in the first study of this thesis it was examined how visuo-vestibular conflicts influence body ownership, a core feature of bodily self consciousness. While participants' subjective experiences remained inconclusive, physiological parameters indicated a stronger body ownership over a fake body during the induction of visuo-vestibular conflicts.

In a second study, we examined the implicit perception of complete and amputated bodies in individuals with a peculiar disorder of bodily self consciousness. We showed that in comparison to amputees and normally-limbed controls, individuals with this disorder prefered amputated bodies. This result mainly demonstrates the risks of using simplified models of bodily self consciousness to explain complex bodily disorders.

Pain perception is an important process in body representation and perception. Thus, in a third study, we investigated whether natural vestibular stimulation would alter pain thresholds, as the analgesic effect of artificial vestibular stimulation has been shown previously. Here, we found that natural vestibular stimulation increased pain thresholds, but so did the control conditions.

Overall, the studies contribute to a better understanding of the influence of the vestibular system on body representation and bodily self consciousness.

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Part I

THEORETICAL BACKGROUND

1 INTRODUCTION

Humans' ability to experience a *self*, has always been fascinating mankind and in philosophy, psychology and neuroscience its relation to the physical body has been a constant topic of debate. The experience of the world as a 'self' located in a fixed body is taken for granted and rarely questioned as it is always there (James, 1890; Merleau-Ponty, 1945). Thus, the body is both, the object in the external world we know best (Ferrè & Haggard, 2016) as well as the vehicle for the self to experience the objects in the world (Gallagher, 2005; Merleau-Ponty, 1945).

An important distinction has to be made between the *narrative* and the *minimal* self (Gallagher, 2000). While psychology has generally been more interested in the *narrative* self defined by higher level aspects such as memory, language and personality, over the last 20 years philosophical and neurocognitive theories fueled each others and presented models of a *minimal* self, where the self is rooted within cortical networks representing the body and influence the *narrative* self (Gallagher, 2000; Blanke & Metzinger, 2009; Berlucchi & Aglioti, 2010; Gallagher, 2005; Botvinick & Cohen, 1998; Blanke, 2012). Blanke & Metzinger (2009) coined the term 'minimal phenomenal selfhood' (MPS) as the conscious experience of being a self and the simplest form of self-consciousness. Crucial features of MPS are a holistic identification with the body (**body ownership**), the experienced **self-location** of the self and third, the **first-person perspective**.

In this thesis, first I will elucidate the mechanism for the above defined bodily self and the crucial features of MPS by the means of multisensory integration and its neural foundations. I will then review how experimental manipulations of bodily self consciousness first focused on body parts, despite the claim that only whole body illusions can capture its global character (Blanke & Metzinger, 2009). In a second step, I will describe distorted experiences of the bodily self in neurological and psychiatric patients. As a case in point, the phenomenon of xenomelia will be discussed in more detail. In a last step, I will focus on the vestibular system and its role in features of the MPS such as self-location and first-person perspective, and its involvement in a disrupted bodily-self consciousness. In this context, I will also comment on the influence of vestibular cues on lower-level processes such as pain perception (Ferrè & Haggard, 2016, for a review).

2 MULTISENSORY INTEGRATION

The core mechanism that enables bodily self consciousness relies on multisensory integration (Blanke, 2012; Blanke, Slater, & Serino, 2015). Multisensory integration describes the process of merging single noisy but redundant sensory input of different modalities to create a limited but understandable and coherent representation of the environment (Fetsch, DeAngelis, & Angelaki, 2013). The variance and thus uncertainty about the world is reduced by the integration of different sensory systems. Perceptual cues are weighted according to their reliability with the visual modality usually dominating other senses (Ernst & Bülthoff, 2004).

2.1 EXPLAINING BODILY SELF CONSCIOUSNESS

Adapted to bodily self consciousness, a continuous integration of bodily signals from different body related senses is required to maintain a stable and coherent representation of the body in its environment (Tsakiris, 2016; Blanke, 2012; Blanke & Metzinger, 2009). The dynamic nature of this processes also implies that bodily self consciousness can be altered with so called multisensory conflicts. Probably the first scientific report of multisensory conflicts altering bodily self perception was introduced by Stratton (1899), who built a complex mirror-device allowing him to see his moving body from a third person perspective above his head. He thus created a conflict between the felt position and the seen position of his body.

2.1.1 *The Rubber Hand Illusion*

In the last 20 years, interest and research in the field of bodily self consciousness were fueled by the famous Rubber Hand Illusion (RHI) (Botvinick & Cohen, 1998). In this paradigm, an illusory ownership over an artificial upper limb is induced through a synchronous tactile stimulation of the unseen own hand and a fake visible rubber hand that leads to a conflict between vision, touch and proprioception, with vision dominating the other signals. To solve this multisensory conflict, participants usually develop an illusory ownership over the rubber hand, and, more implicitly, perceive their hand's position measurably displaced towards the rubber hand (proprioceptive drift). This illusion has been successfully applied to other multisensory conflicts (Tsakiris, Prabhu, & Haggard, 2006; Capelari, Uribe, & Brasil-Neto, 2009; Suzuki, Garfinkel, Critchley, & Seth, 2013; Walsh, Moseley, Taylor, & Gandevia, 2011; Ehrsson, Holmes, & Passingham, 2005; Senna, Maravita, Bolognini, & Parise, 2014). Different attempts have been made to characterize the neural correlates of the RHI (for an overview see Figure 1): for the contrast of synchronous stroking versus asynchronous stroking (control condition), several functional Magnetic Resonance Imaging (fMRI)-studies (Bekrater-Bodmann et al., 2014; Limanowski et al., 2014; Ehrsson et al., 2004) and one Positron Emission Tomography (PET)-study (Tsakiris et al., 2007) revealed brain areas such as the bilateral anterior insula (Limanowski et al., 2014; Ehrsson et al., 2004) the left extrastriate body area (Limanowski et al., 2014), the bilateral frontal operculum (Ehrsson et al., 2004), the premotor cortex (Bekrater-Bodmann et al., 2014; Ehrsson et al., 2004), and the middle (Tsakiris et al., 2007) and the posterior (Ehrsson et al., 2004) cingulate cortex. Correlations between (indirect) brain activity and the illusion strength of the RHI uncovered a significant relationship in the left extrastriate body (Limanowski et al., 2014), the bilateral premotor cortex (Bekrater-Bodmann et al., 2014; Ehrsson et al., 2004). Moreover, Tsakiris and colleagues (2007) reported a significant correlation between the amount of proprioceptive drift and the activity in the right frontal operculum, the right posterior insula, the middle frontal gyrus, the left parietal operculum, the left postcentral gyrus, the left hippocampus and the right posterior cingulate cortex.

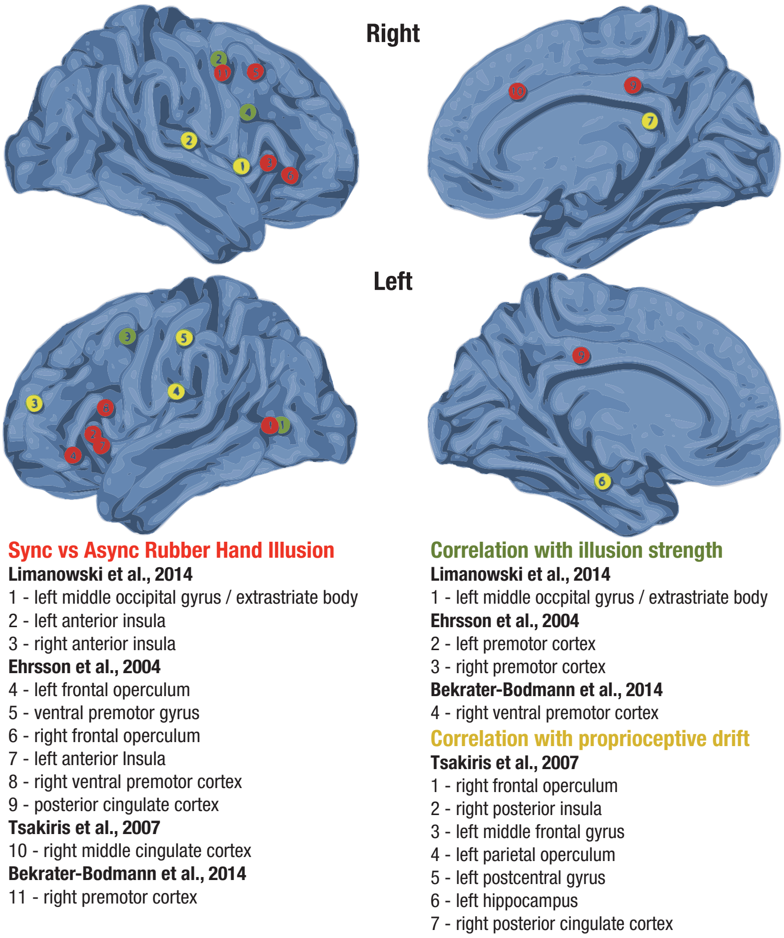

Figure 1: Self-created illustration for Lenggenhager & Lopez (2015). An overview of neuroimaging studies conducted to reveal neural correlates of the RHI (Ehrsson et al., 2004; Bekrater-Bodmann et al., 2014; Limanowski et al., 2014; Tsakiris et al., 2007). Red dots indicate significant brain activation in the comparison of synchronous visuo-tactile stimulation to asynchronous visuo-tactile stimulation. Green dots indicate brain areas where brain activity was related to the strength of the RHI. Yellow dots show areas that were significantly associated to the proprioceptive drift. For the generation of the figure, MNI coordinates were extracted from the original studies and mapped onto a brain template with Caret (http://www.nitrc.org/projects/caret/ (Van Essen, 2012)).

2.1.2 *Full Body Illusions*

Unfortunately, the RHI only focuses on a body part and thus neglects the global and unifying character of the bodily self consciousness (Aspell, Lenggenhager, & Blanke, 2012; Blanke & Metzinger, 2009). Other multisensory conflict evoking paradigms such as the Full Body Illusion (FBI) (Lenggenhager et al., 2007) and the Body Swap Illusion (Petkova & Ehrsson, 2008) (see also Figure 2 on the left for an illustration of the illusions) have been developed and successfully manipulated more global aspects of the the bodily self, such as the perceived self-location (Lenggenhager et al., 2007). Importantly, it is argued that only those paradigms can investigate MPS (Blanke & Metzinger, 2009). In such paradigms, a participant typically sees his body through a head-mounted display (HMD) attached to a recording device while being touched. The congruence of visual (touched own body seen through HMD) and tactile (being touched) leads to a multisensory conflict, which is solved by experiencing the self location closer towards the 'virtual' body. As for the RHI, this so-called Full Body Illusions (FBI) have been replicated with other multisensory conflicts such as between the visual and cardiac (Aspell et al., 2013), visual and sensorymotor (Kannape, Schwabe, Tadi, & Blanke, 2010), and visual and respiratory (Adler, Herbelin, Similowski, & Blanke, 2014) modalities.

Manipulations of the perceived self location and the experienced first person perspective induced by the FBI triggered neural activity in the bilateral extrastriate body area, the bilateral postcentral gyrus, the occipital lobe, and most interesting in the temporo-parietal junction (TPJ) bilaterally (see also Figure 2) (Ionta et al., 2011). An attempt to describe the underlying functional connectivity of an FBI showed that the temporal BOLD-signal in the bilateral TPJ correlates with the ventral premotor cortex, the insula and the supplementary motor areas (Ionta, Martuzzi, Salomon, & Blanke, 2014). In contrast, the Body Swap Illusion elicited more brain activity in the bilateral ventral premotor cortex (Petkova et al., 2011), the extrastriate body area and the posterior cingulate cortex (Guterstam, Björnsdotter, Gentile, & Ehrsson, 2015) and other areas that are not discussed here. In conclusion, activation patterns depended strongly on the used experimental paradigm. This difference in brain activity might be related to the different perspectives, from which a fake or the own body is seen: while the FBI mainly induces a change in self location, the Body Swap Illusion elicits a stronger feeling of body ownership. Interestingly, the FBI and Body Swap Illusion share activation the extrastriate body area.

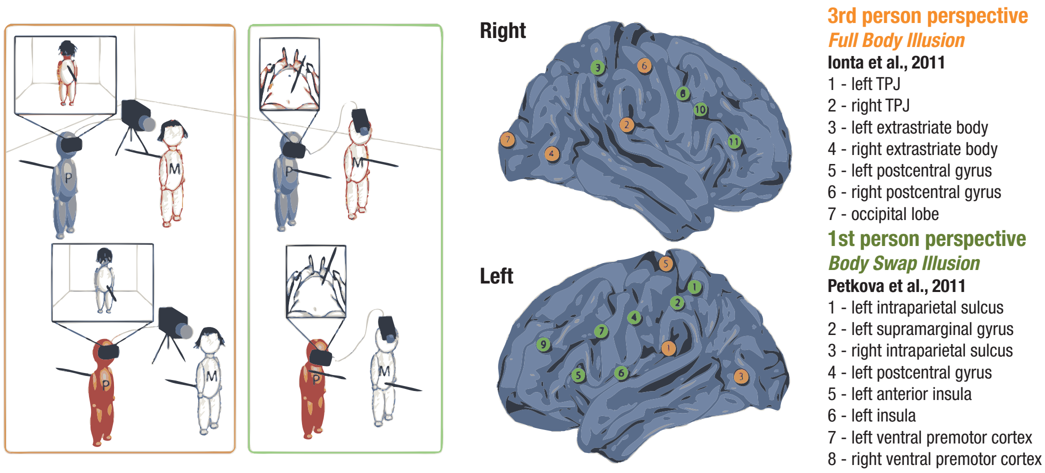

Figure 2: Self-created illustration for Lenggenhager & Lopez (2015). A comparison of brain activity associated to the FBI (Lenggenhager et al., 2007, setup in orange frame) and the Body Swap Illusion (Petkova & Ehrsson, 2008, in green frame). The locus of self-identification is indicated in red. Two fMRI studies using either the FBI (Ionta et al., 2011, in orange circles) or the Body Swap Illusion (Petkova et al., 2011, in green circles) are compared. Only areas significantly more activated during synchronous visuo-tactile stimulation as compared to control conditions are shown. For the generation of the figure, MNI coordinates were extracted from the original studies and mapped onto a template with caret (http://www.nitrc.org/projects/caret/ (Van Essen, 2012)). Adapted from Serino et al. (2013) Figure 2.

2.2 DISTURBED BODILY SELF CONSCIOUSNESS

Next to the experimental manipulations described above, the fragility and malleability of bodily self consciousness have been observed in several psychiatric and neurological disorders (Brugger & Lenggenhager, 2014; Critchley, 1950, see). Phenomena affecting body parts such as somatoparaphrenia (Vallar & Ronchi, 2009), the lack of ownership over a limb mostly after a right parietal and insular insult, or phantom limb sensations (Melzack, 1992), the feeling of ownership over a body part that it is physically absent, have inspired the RHI. As a case in point, in this thesis I will focus on xenomelia (McGeoch et al., 2011) or Body Integrity Identity Disorder (BIID) (2005), a condition that in the last few years has received growing attention from neuroscience and psychiatry (Brugger, Christen, Jellestad, & Hänggi, 2016), but also from popular media (Ananthaswamy, 2015).

2.2.1 *Xenomelia*

In xenomelia, otherwise healthy individuals describe a feeling of "overcompleteness" of the physicial body as opposed to the person's body image (Ramachandran, Brang, McGeoch, & Rosar, 2009; Brugger, Lenggenhager, & Giummarra, 2013), leading to a strong desire for the amputation of the afflicted limb.

In extensive surveys First (2005) identified several crucial descriptors such as higher prevalence in men, a dominance of the left leg, onset in early childhood, an unusual admiration of amputees' bodies, in some cases even accompanied by sexual attraction, and a pretending to be an amputee behaviour. He consequently characterized xenomelia as a failure to develop a fundamental anatomical bodily identity.

Due to its similarity to neurological disturbances of the bodily self such as somatoparaphrenia (Romano, Sedda, Brugger, & Bottini, 2015), misoplegia (hatred for a body part) (Loetscher, Regard, & Brugger, 2006) and asomatognosia (the felt absence of a limb) (Dieguez, Staub, & Bogousslavsky, 2007), there has been a growing interest in revealing neural correlates of xenomelia. Neurophysiological (McGeoch et al., 2011), structural and functional neuroimaging (Hilti et al., 2013; van Dijk et al., 2013) studies were able to pinpoint altered neural responses and gray matter in the right parietal lobe and the right insula in participants with BIID. Somatoparaphrenia has also been associated to neural damage in the right parietal lobe and the right posterior insula (Ramachandran & McGeoch, 2007; Baier & Karnath, 2008). Undoubtedly, these neural correlates are crucial to understand the complex nature of xenomelia, but they also bear risks (Fisher & First, 2011): They can mislead the general opinion to interpret correlations as causality, mostly neglecting the possibility of experience dependent neural plasticity (Brugger et al., 2013).

2.3 THE VESTIBULAR SYSTEM & BODILY SELF CONSCIOUSNESS

Although previous research has put strong emphasis on vision and touch, bodily self consciousness is characterized by spatial phenomena such as self location and a first-person perspective (Pfeiffer, Serino, & Blanke, 2014). The vestibular system is arguably the most essential sensory modality for these components as it encodes the head position, movement in space and thus its orientation in the environment (Lenggenhager & Lopez, 2015; Lopez, Halje, & Blanke, 2008). As part of the inner ear, it consists of the otoliths (utricle and saccule) that code linear acceleration and the semicircular canals sensing rotation acceleration in the three-dimensional space (Pfeiffer et al., 2014). In contrast to other sensory modalities, vestibular signals are coupled to other sensory cues at an early stage before even reaching the cortex. Thus, there is no pure vestibular cortex as analogy to the primary cortices for audition, somatosensation and vision (Lopez, Blanke, & Mast, 2012; Pfeiffer et al., 2014; Blanke, 2012). These early couplings are essential for gaze control and eye fixation for example while walking. In a recent review, Ferrè & Haggard (2016) present a compelling hierarchical overview on how the vestibular system influences body perception and representation. It is summarized in Figure 3 and will be discussed in more detail near the end of this section.

2.3.1 *The vestibular system and bodily illusions*

The most compelling evidence for the involvement of the vestibular system in bodily self consciousness is build upon observations of neurological patients with Out of Body Experiences (OBE) (De Ridder, Van Laere, Dupont, Menovsky, & Van de Heyning, 2007; Blanke, 2004; Blanke & Mohr, 2005; Ionta et al., 2011; Blanke, Ortigue, Landis, & Seeck, 2002). OBE is the most prominent representative from a group of distinct disturbances that lead to a disruption of central aspects of bodily self consciousness and are summarized as autoscopic phenomena (Brugger, Regard, & Landis, 1997; Brugger, 2002; Lopez et al., 2008; Blanke & Mohr, 2005). In autoscopic phenomena, individuals experience the illusion of seeing the own body in the extrapersonal space. More specificly, OBEs are characterized by the experience that the self is localized out of one's body, and the vision of the world and one's own body is perceived from an extracoporeal position (Blanke, 2004). They usually can be evoked by stimulation (Blanke et al., 2002), a lesion (Ionta et al., 2011) or dysfunction (Blanke, 2004) of the TPJ, a region that is also part of the vestibular cortex (Lopez et al., 2008; Lopez et al., 2012). Also, they are usually associated with vestibular sensations such as flying and floating (Blanke, Landis, Spinelli, & Seeck, 2004), which suggests a failed integration of propropceptive, tactile, visual, extrapersonal space and in particular vestibular input in the TPJ during an OBE. The FBI (Lenggenhager et al., 2007) allows to simulate aspects of an OBE (e.g. change in self location) in healthy participants.

To understand how humans perceive their body, it is important to consider that human consciousness was shaped in a constant terrestrial gravitational field, i.e. a constant linear acceleration (Lenggenhager & Lopez, 2015; Blanke, 2012) and heavily relies on internal models of gravity (Indovina et al., 2005). In fact, in microgravity the otolithic organs are deafferented and participants of such parabolic flights report an illusion of body orientation inversion, which is described as the feeling of the body being upside-down relative to the extrapersonal space (Lackner, 1992; Blanke, 2012). This also implies that the otoliths as indicators of orientation are confronted with ambiguity due to same stimulation patterns evoked by the gravitational force as well as other translation acceleration (MacNeilage, Banks, Berger, & Buelthoff, 2007). Usually the ambiguity is solved by the integration of visual and somatosensory signals. Accordingly, a more elaborated Bayesian model could simulate OBEs as the result of the misguided misguided integration between ambiguous bottom up vestibular signals from the otoliths in the supine position and top-down priors from a standing position (Schwabe & Blanke, 2008).

The involvement of the vestibular system in bodily disorders has been observed and reported even in Ancient Greece (Grabherr, Macauda, & Lenggenhager, 2015). More than 100 years ago, Bonnier (1905) described that vestibular stimulation, i.e. head shaking, decreased bodily illusions in vestibular patients. Thus, vestibular stimulation has enthusiastically been proposed as treatment for various bodily disorders (Grabherr et al., 2015). I his book 'l'aschemtic', Bonnier (1905) also observed that patients with vestibular disorders experienced their face or other body-parts illusory enlarged, a phenomenon that is known as macrosomatognosia. In fact, in a recent case study it was shown that Caloric Vestibular Stimulation (CVS) abolished macrosomatognosia transientlly (Rode et al., 2012). CVS stimulates the semicircular canals through the irrigation of cold or warm water into the external ear canal. Rode and colleagues (2012) suggest that vestibular stimulation may act upon cerebral structures involved in the process of creating and updating of body parts representations. Similarly, it has been shown that CVS lead to a (partial) remission of somatoparaphrenia (Bisiach, Rusconi, & Vallar, 1991; Rode et al., 1992). Inspired by this finding and due to shared aspects of somatoparaphrenia and xenomelia, Ramachandran and McGeoch (2007) proposed CVS as a potential treatment for xenoemlia, which we have shown to be ineffective in a first stimulation attempt using CVS (Lenggenhager, Hilti, Palla, Macauda, & Brugger, 2014). This finding shows that caution is needed when proposing therapeutic brain stimulation in complex disorders such as xenomelia based solely on a simplified neurological model. In fact, several findings/symptoms do not easily fit a one-to-one comparison of xenomelia to neurological disorders of the bodily self, such as spontaneous remission in somatoparaphrenia patients, the amputation desire not only being limited to the left body side and heterogeneity in xenomelia reports (Sedda, 2011).

2.3.2 *Vestibular bodily self consciousness in Healthy Participants*

Observations in patients are informative and useful for theory development but are not best suited for theory testing for several reasons. False hopes may arise that experiments may actually have a positive effects on the patient's conditions. Second, specific patient populations are usually rather small and heterogeneous, which makes it difficult to detect statistically small or even medium effects with conventional approaches such as Null Hypothesis Testing. Thus, to investigate the influence of the vestibular system on aspects of bodily self consciousness experimental paradigms for healthy participants are indispensable.

Along these lines, in the already mentioned FBI study adapted for fMRI, Ionta and colleagues (Ionta et al., 2011) observed that despite identical viuotactile stimulation some of the participants experienced looking downwards on a fake body, while others experienced looking upward. Interestingly, in their study visual cues of the fake body implied a downward directed first person perspective while participants were lying in a supine position. This difference in perceived self location of the first person perspective was associated with Blood Oxygen Level Dependent (BOLD)-signal changes in the TPJ. Following up on this finding, Pfeiffer and colleagues (2013) manipulated the degree of visuo-vestibular conflicts. They showed that bodily self consciousness depends on visual gravitational information and that individual differences in visuo-vestibular integration correlated with the experienced direction of the first-person perspective. Using a graphestesia task to measure embodiment, where ambiguous letters such as 'b' or 'd' are drawn to the forehead and can either be perceived from an 'inside' (first person) or an 'outside' (third person) perspective, it has been shown that additional vestibular input delivered by Galvanic Vestibular Stimulation (GVS) increased the perceived first person perspective and it is thus argued that weak vestibular stimulation anchors the body to the self (Ferrè, Lopez, & Haggard, 2014). In GVS two electrodes are pleased on the mastoid processes, between which a weak current is then applied. The exact eliciting mechanism of this vestibular stimulation is unknown, but it is thought to stimulate the otoliths and the semicircular canals (Fitzpatrick & Day, 2004). Normally, it is used to induce additional vestibular noise.

GVS was also used to manipulate body ownership over specific body parts. In an adaptation of the RHI, Lopez, Lenggenhager & Blanke (2010) set out to investigate vestibular contributions to the perceived ownership of body parts in healthy participants and found that left anodal GVS increased illusory ownership over a fake hand as compared to no stimulation.

2.3.3 *The Importance of the Vestibular System in Spatial Navigation*

Observations in patients with peripheral vestibular and concomitant deficits in spatial cognition, i.e. spatial navigation and memory (Brandt et al., 2005), indicate the importance of vestibular processes on spatial cognition. Thus, the vestibular system is not only processing motion in the physical world, but is also suggested to possess a covert mode of functioning to build and maintain a mental representation of the physical world (Mast & Ellis, 2015; Mast, Preuss, Hartmann, & Grabherr, 2014).

Such a representation is needed in mental transformation processes that rely on spatial cognition, especially when simulated changes in self location are necessary. This theory has been put to test in several experiments involving the mental transformation of body shaped stimuli under the influence of vestibular stimulation (Lenggenhager, Lopez, & Blanke, 2008; Falconer & Mast, 2012; van Elk & Blanke, 2014; Grabherr & Mast, 2010; Dilda, MacDougall, Curthoys, & Moore, 2011). While congruent motion induced by natural vestibular stimulation (van Elk & Blanke, 2014) or CVS (Falconer & Mast, 2012) facilitated own body transformations, perceived vestibular noise or the lack of vestibular input impaired egocentric mental transformations, but not object based mental transfromations (Dilda et al., 2011; Lenggenhager et al., 2008; Grabherr & Mast, 2010). Interestingly, egocentric mental rotation has also been associated to the bilateral TPJ and the extrastriate body area (Blanke & Mohr, 2005; Arzy, Thut, Mohr, Michel, & Blanke, 2006; Aichhorn, Perner, Kronbichler, Staffen, &

Ladurner, 2006). The conclusion of these few studies is incoherent and further high-powered studies are necessary to gain more specific knowledge about the underlying mechanisms.

2.3.4 *A Model of the Vestibular influence on body representation*

In a recent review, Ferrè & Haggard (2016) describe three hierarchical levels of body representation, upon which the vestibular system can act (see also Figure 3). So far in this section, the presented evidence for the involvement of the vestibular system in bodily self consciousness focused exclusively on somatorepresentation.

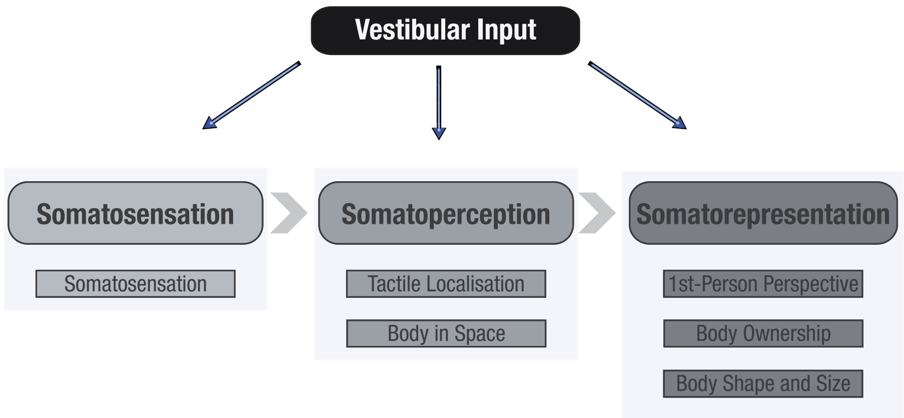

Figure 3: Adapted from Ferrè & Haggard (2016). The illustration shows how the vestibular system independently influences hierarchical levels of body representation and their processes. From left to right the level of higher-order processes is ascending. Each level depends on its predecessors. Somatosensation constitutes the lowest level, which is involved in primary sensory processing. At the level of somatoperception percepts of somatic objects are formed. At the highest level, the so-called somatorepresentation, knowledge about the body as a physical object in the world is represented.

Ferrè & Haggard (2016) present an extensive overview on how CVS and GVS restore somatosensory deficits in mostly neurological patients and enhances somatosensation in healthy participants. There are multiple explanation models but the exact underlying mechanisms are unclear. Within somatosensation, it has been suggested for more than 2000 years that vestibular stimulation could ameliorate pain (Grabherr et al., 2015). In two recent studies, CVS has been shown to modulate thermal pain perception (Ferrè, Bottini, Iannetti, & Haggard, 2013; Ferrè, Haggard, Bottini, & Iannetti, 2015). The latter study showed a CVS-specific analgesic effect upon arrival of the nociceptive input in the primary somatosensory cortex (Ferrè et al., 2015). However, the analgesic effect has been proposed before the invention of CVS and it is thus unclear whether there is a vestibular stimulation type independent effect on pain perception, i.e. whether natural vestibular stimulation would similarly reduce pain.

3 AIMS & RESULTS

The aims of this thesis are threefold with the broad overarching theme of the influence of the vestibular system on various aspects of body representation: In a first step, a classical version of a body swap illusion was used in a way that the visuo-vestibular congruency was manipulated (Macauda et al., 2015). This is the first study that tested the direct influence of visuo-vestibular integration on full body ownership. The starting point for the second aim was set by null findings found by our group in a previous explorative vestibular stimulation study in individuals with xenomelia (Lenggenhager et al., 2014). The study tested the specific hypothesis that proposed the therapeutical use of CVS in xenomelia (Ramachandran & McGeoch, 2007). This null finding suggested a refinement of the etiology and underlying mechanisms of xenomelia. Thus, in a second step, this thesis aimed to explore social aspects of body representations, specifically in individuals with xenomelia (Macauda, Bekrater-Bodmann, Brugger, & Lenggenhager, 2017), and thus followed the general trend in multisensory research to study social parameters of bodily self consciousness (Lenggenhager & Lopez, 2015; Deroualle & Lopez, 2014; Maister, Slater, Sanchez-Vives, & Tsakiris, 2015). The third aim was fueled by the hypothesized analgesic effect of vestibular stimulation, which we critically discussed in a historical review on the therapeutical use of vestibular stimulation (Grabherr et al., 2015). Based on two recent experiments that studied the pain-modulating effect of CVS (Ferrè et al., 2013, 2015), this third step aimed to study the effect of natural vestibular stimulation on pain perception and processing (Macrea et al., 2016).

As described throughout the introduction, body representation is highly influenced by the vestibular system (see also Figure 3) (Ferrè & Haggard, 2016). In this study (Macauda et al., 2015), a focus was placed on somatorepresentation and studied the impact of visuo-vestibular conflicts on body ownership. Visuo-tactile body swap illusions (see also Figure 2), have been proven a successful paradigm to induce body ownership over a fake body (Petkova & Ehrsson, 2008). To study the influence of the vestibular system, in the present study a Body Swap Illusion with visuo-vestibular conflicts was used to induce body ownership over a mannequin's body. An illusion concerning the full body was chosen as the vestibular system is supposed to influence global aspects of bodily self consciousness such as self location in space, which cannot be captured by body part illusions (e.g. the RHI).

The visuo-vestibular congruence was manipulated with a six-degree of freedom motion platform located at the University Hospital of Zurich and with the use of virtual equipment (see also study 1 in the empirical part). In a within subject design, participants were seated in the centre of the motion platform. The fake body (mannequin) and a control object were positioned on the motion platform and filmed with a web cam attached above the motion platform. The resulting video feed of a moving mannequin/object was presented to 21 healthy participants either in real time or with a temporal delay over a Head Mounted Display (HMD). In the congruent condition, the seen movement matched the experienced motion. In the incongruent condition, there was a dissociation between what participants saw and what their vestibular system perceived. Participants underwent four different conditions.

To explicitly measure the effects of the illusion, classical questionnaires were used(Botvinick & Cohen, 1998; Lenggenhager et al., 2007). In the last few years, skin temperature changes have been used as a proxy for implicit changes of body ownsership induced by multisensory conflicts (Salomon, Lim, Pfeiffer, Gassert, & Blanke, 2013; Moseley et al., 2008). Thus, three thermo-couples were attached to the participants' hands and neck. It was predicted that participants should most identify with the mannequin's body when the visuo-vestibular input was congruent. Further, it was predicted that the identification would be accompanied by a decrease of the skin temperature.

The statistical analysis of this first study showed that participants only weakly identified with the mannequin's body and had difficulties in detecting visuo-vestibular incongruence. However, a skin temperature decrease of the hands was visible in the visuo-vestibular congruent mannequin condition. This result was interpreted as an implicit change of body ownership over the fake body. The failure to strongly identify with a mannequin was suggested to be partly caused by the inability to detect visuo-vestibular incongruence. In summary, evidence was provided that visuo-vestibular conflicts indeed influence body ownership, but new questions arose.

3.2 STUDY 2: WHEN LESS IS MORE

Based on shared aspects of somatoparaphrenia and xenomelia Ramachandran and McGeoch (2007) proposed CVS as a potential treatment for xenoemlia. A previous study in our lab tested this hypothesis in thirteen individuals with xenomelia, i.e. an amputation desire directed to the lower limb(s) (Lenggenhager et al., 2014). Contrary to prediction, CVS did not result in a qualitative reduction of the amputation desire. This negative finding may have many reasons. First, xenomelia is more complex than somatoparaphrenia. The comparison to somatoparaphrenia may be useful to illustrate aspects of the phenomenology, but at the same time bears the risk of an oversimplification of the phenomenon. While somatoparaphrenia occurs after brain damage, individuals with xenomelia report a start of their amputation desire in early childhood. Thus, many other components may shape body representation in individuals with xenomelia. Supposedly, an important factor in a model of xenomelia are social aspects (Brugger et al., 2013). Several lines of research have shown that social processes shape body perception and representation (Maister et al., 2015).

In a similar vein, explicit questions may not be sensitive to measure amputation desire in xenomelia. Thus, in study 2 those two lines of reasoning were combined. The aim was to examine the implicit attitude versus amputated and complete bodies and compare those attitudes to explicit ones. To measure implicit attitudes a widely used tool from social psychology was used: the Implicit Association Test (IAT) (Greenwald, McGhee, & Schwartz, 1998). The prevalence of xenomelia is still unknown. However, over the last few years internet provided individuals with xenomelia the necessary infrastructure to create dedicated discussion groups. To gather meaningful data in individuals, the presented study opted for an online version of the IAT to reach more participants. This strategy enabled the recruitment of almost 50 participants with xenomelia, of whom 34 were included in the study. Next to normally-limbed participants as a control group, participants who underwent an amputation were recruited. The recruitment of the amputees was based on a large database that was accessed by Robin Bekrater-Bodmann from the University of Heidelberg. Data were analysed in a Bayesian framework as an a priori power analysis to establish the required sample size was not possible. Thus, hypotheses were evaluated based on the present data.

As predicted, normally-limbed participants had a more implicit preference for complete bodies than participants with an amputation desire. Interestingly, also amputees showed the same pattern compared to participants with xenomelia. The results indicated a slight implicit preference for amputated bodies in individuals with an amputation desire. Unsurprisingly, individuals with xenomelia explicitly preferred amputated bodies, while the opposite pattern was found in normally-limbed participants and amputees. In general, the study provided an illustration of social aspects involved in the formation of body representation.

3.3 STUDY 3: REDUCING PAIN BY MOVING?

In this third study, the effects of natural vestibular stimulation on somatosensation, i.e. pain processing were tested. The analgesic effect of vestibular system has been proposed and widely used (e.g. hangig beds) for over 2000 years (Grabherr et al., 2015). Recently, two studies addressed the question experimentally and applied artificial vestibular stimulation (CVS) while inducing thermal pain (Ferrè et al., 2013, 2015). However, next to strong peripheral vestibular stimulation, CVS also elicits strong illusory self-motion and mostly vertigo (Lopez & Blanke, 2014). In the light of physiological differences in different vestibular stimulation techniques (Palla & Lenggenhager, 2014), it is crucial to have more insight into the working mechanisms to propose vestibular stimulation as potential pain treatment. Moreover, the study tested whether potential analgesic effects were due to the effects of vestibular stimulation or to the illusion of moving. To examine this question visual optokinetic stimulation was applied (Brandt, Dichgans, & Koenig, 1973).

In twenty healthy men, natural vestibular stimulation (head and body motion on a rotation chair) was applied in combination with a standardized method to induce thermal pain (Maier et al., 2010). The experiment also included quantitative sensory testing. Pain-evoked potentials were measured as well(see Appendix for the Supplementary Material of this study). For the natural vestibular stimulation, participants were restrained on a 3D-chair at the University Hospital of Zurich. Different sinusoidal movement patterns were used. Optokinetic stimulation was delivered through a HMD by the means of white dots moving either coherently to the left, to the right or at random (no stimulation). A detailed experimental design is illustrated in Figure 10. Interestingly, compared to a baseline all interventions reduced the perceived pain, even the random dots.

In conclusion, the study suggested that vestibular and visual stimulations significantly increased heat pain thresholds. The results suggested non specific attentional effects rather than stimulation effects as even random dots increased the heat pain threshold.

Part II

EMPIRICAL STUDIES

*shared first-authorship

4

STUDY 1: BINDING BODY AND SELF IN VISUO-VESTIBULAR CONFLICTS

ABSTRACT

Maintenance of the bodily self relies on the accurate integration of multisensory inputs whereby visuo-vestibular cue integration is thought to play an essential role. Here, we tested in healthy volunteers how conflicting visuo-vestibular bodily input might impact on body-self coherence in a full body illusion set-up. Natural passive vestibular stimulation was provided on a motion platform, while visual input was manipulated using virtual reality equipment. Explicit (questionnaire) and implicit (skin temperature) measures were employed to assess illusory self-identification with either a mannequin or a control object. Questionnaire results pointed to a relatively small illusion, but the hand skin temperature, plausibly an index of illusory body ownership, showed the predicted drop specifically in the condition when participants saw the mannequin moving in congruence with them. We argue that this implicit measure was accessible to visuo-vestibular modulation of the sense of self, possibly mediated by shared neural processes in the insula involved in vestibular and interoceptive signaling, thermoregulation and multisensory integration.

4.1 INTRODUCTION

The sense of the "self" and its relation to the body has always fascinated mankind and has increasingly been studied in empirical research. Recent models suggest that the self is grounded in neural mechanisms representing the body, and thus crucially relies on successful multisensory integration for a review see (for a recent review see Blanke, 2012). Failure of such integration results in disturbances of the bodily self, apparent in various neurological and psychiatric conditions (e.g. somatoparaphrenia and autoscopic phenomena, see Brugger & Lenggenhager, 2014, for a recent review) . Experimental evidence further shows that the bodily self can be manipulated in systematic and predictable ways by introducing a conflict between two or more sense modalities. During spatially conflicting body-related information, one sensory system (e.g. vision) dominates the information from other sensory modalities (e.g. proprioception or touch). This might result in an illusory ownership for a body part, e.g. a seen fake hand (Botvinick & Cohen, 1998), foot (Lenggenhager, Hilti, & Brugger, 2015), face (Tsakiris, 2008; Sforza, Bufalari, Haggard, & Aglioti, 2010) or even a full body (Lenggenhager et al., 2007; Petkova & Ehrsson, 2008). These illusions have been linked to specific properties of multimodal neurons (e.g. Graziano & Botvinick, 2002) and involve a network of premotor, temporo-parietal and insular areas (Blanke, 2012) (for recent reviews see Lenggenhager & Lopez, 2015).

The conflicts inducing body part and full body illusions (FBI) initially involved the visual and tactile modalities. Specifically, felt touch on an unseen body part in synchrony with visually observed touch on a corresponding artificial body part led to an illusory feeling of ownership for the latter (Botvinick & Cohen, 1998). Recent publications have employed conflicts between other modalities were also employed, e.g. between visual and sensorimotor (Tsakiris et al., 2006; Kannape et al., 2010), visual and nociceptive (Capelari et al., 2009), visual and cardiac (Aspell et al., 2013; Suzuki et al., 2013), visual and respiratory (Adler et al., 2014), visual and proprioceptive (Walsh et al., 2011), proprioceptive and tactile (Ehrsson et al., 2005) or auditory and tactile (Senna et al., 2014) information.

No study so far has tried to induce bodily illusions by manipulating the information deriving from concurrent stimulation of the visual and vestibular senses. This is surprising, as an increasing number of clinical observations have suggested a critical role of visuo-vestibular integration for binding body and self (in the context of out of body experiences: Devinsky, Feldmann, Burrowes, & Bromfield, 1989; Blanke et al., 2002, 2004; Blanke, 2004; Brandt, Brechtelsbauer, Bien, & Reiners, 2005; De Ridder et al., 2007; Ionta et al., 2011; Mazzola et al., 2014). Likewise, experimental findings point to a crucial contribution of the vestibular system to the bodily self (for recent reviews see e.g. Lenggenhager, Smith, & Blanke, 2006; Lopez et al., 2008; Blanke, 2012; Lopez, 2013; Pfeiffer et al., 2014). For the latter, mental simulation of changes in self-location and disembodiment (i.e. own-body transformation) can be markedly altered during vestibular stimulation (Lenggenhager et al., 2008; Falconer & Mast, 2012; van Elk & Blanke, 2014), and importantly, this applies only to full bodies but not to body parts. Accordingly, functional imaging studies during full body illusions associated illusory changes in first-person perspective and self-location with altered activity and connectivity in the bilateral temporo-parietal junction, a multisensory area which is part of the so-called *vestibular cortex* network (Ionta et al., 2011, 2014).

Visuo-vestibular cue integration is essential for self-motion, motor control, and spatial orientation and hence for the interaction with our environment (for a review see Fetsch, DeAngelis, & Angelaki, 2010) and the demarcation of self from non-self (Lopez, 2013). Visuo-vestibular cues are normally merged in a statistically optimal fashion, with vision helping to discriminate ambiguous vestibular signals, and also vice versa (MacNeilage et al., 2007; Fetsch, Turner, DeAngelis, & Angelaki, 2009; Berger, Schulte-Pelkum, & Bülthoff, 2010; Butler, Campos, Buelthoff, & Smith, 2011; Butler, Campos, & Buelthoff, 2015; Prsa, Gale, & Blanke, 2012).

In view of the strong link between the vestibular system and aspects of the bodily self, we set out to fill the gap in current research using multisensory illusions by testing visuo-vestibular cue integration in a FBI setup. Following the paradigm of previous FBI studies (Petkova & Ehrsson, 2008), participants observed either a body (mannequin) or an object moving with respect to the ground from first-person perspective through a head mounted display (HMD). This approach complements traditional studies investigating visuo-vestibular cue integration using more general optic flow (MacNeilage et al., 2007; Fetsch et al., 2009; Berger et al., 2010; Butler et al., 2011, 2015; Prsa et al., 2012) and allows to link it more directly to the concept of the bodily self. Congruence between visual and vestibular information was manipulated by altering visual input during passive whole-body movements. Explicit changes in the bodily self were assessed by a questionnaire, while skin temperature was recorded as an implicit measure; previous studies have shown a drop in skin temperature during illusory self-identification with a fake hand (Moseley et al., 2008; Hohwy & Paton, 2010; Kammers, Rose, & Haggard, 2011; Tsakiris, Tajadura-Jimenez, & Costantini, 2011) or an artificial body (Salomon et al., 2013). In accordance with these findings we expected a stronger FBI during visuo-vestibular congruent stimulation of the own body and that of a mannequin. We also predicted an accompanying drop in skin temperature.

4.2 METHODS

4.2.1 *Participants*

Twenty-one healthy volunteers participated in the experiment (13 female, mean age = 25.9 $\pm$ 1.33, 17 right handed). All participants had normal or corrected to normal vision, were fluent in German, reported no history of motion sickness nor of any neurological or psychiatric disorder. The study was approved by the local Ethics Committee and conducted according to the ethical standards of the Declaration of Helsinki. All participants gave written informed consent before the experiment. At the end, participants were debriefed and received a remuneration of 20 Swiss francs.

4.2.2 *Procedure*

4.2.2.1 *General Procedure*

Participants were comfortably seated on a motion platform. Their head was fixed at the back of the seat with a head-shaped pillow and from the sides with two adjustable hard fixation pillows. They were encouraged to relax and not to move during the experiment. Earplugs and white noise presented through headphones were used to cancel out the noise of the motion platform. Participants wore a HMD for the video presentation (see Experimental Setup 4.2.2.2) and were required to keep their hands in the grasping posture around a horizontal pole in front of them, as taken at the begin of the experiment. Thermosensors (see 4.2.3.2 Temperature) were attached to the participants´ hands and neck.

The experiment consisted of four conditions presented in a counterbalanced order. Each condition lasted about two minutes and was followed by a questionnaire displayed on the HMD. After the experiment, participants underwent a semi-structured interview asking about their experiences and thoughts while being seated on the motion platform.

4.2.2.2 *Experimental Setup*

The experiment was conducted on a motion platform with six degrees of freedom (E-Cue 624-1800 motion system, FCS Simulator Systems, Schiphol, Netherlands). The platform delivered a sequence of translational accelerations (ranging from 0.16 $\frac{m}{s^2}$ to 0.9 $\frac{m}{s^2}$) along the earth-horizontal interaural axis lasting between 3 and 12 s for an overall stimulus duration of 120 s (see Figure 4 E/F for the exact motion pattern). This movement pattern, identical for all the participants and conditions, was selected in order to provide a passive vestibular stimulation that was clearly detectable but not nauseating. Capitalizing on results from the rubber hand illusion (RHI), suggesting a stronger illusion when stroking was applied irregularly (Petkova & Ehrsson, 2009), different accelerations and amplitudes (distances) were used within the motion pattern. The seat for the participants was positioned in the center of the platform (Figure 5). A life-size mannequin dressed in white and with realistically looking rubber hands (Figure 4A/B) or a red roundish object of about the same size (Figure 4C/D) was positioned on the posterior part of the platform facing the direction opposite to that of the participant.

EXpyVR (http://lnco.epfl.ch/expyvr) was used for video and questionnaire presentation, and for recording the responses. The movements were filmed with a Logitech c930e webcam (Logitech, Lausanne, Switzerland) with a max-

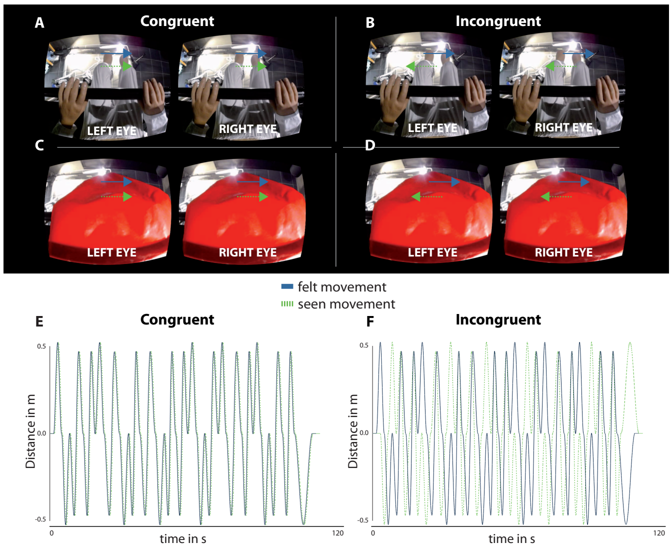

Figure 4: Experimental setup. Overall, the blue arrows and lines indicate the passive movement on the motion platform, which is sensed by the vestibular system while the green arrows and lines represent the seen movement of either the body (A and B) or the object (i.e. a red pillow) (C and D). A - D represent screenshots of the different conditions. E and F represent felt (blue) and seen (green) motion pattern.

imal width of 640 pixels. The video feed was sent to a laptop connected to the HMD (Oculus Rift, Oculus VR, Irvine, USA). The head tracking system implemented in the Oculus Rift was disabled. The video was displayed with a resolution of 1280×768 pixels and an approximately 90° field of view in the horizontal plane. Participants responded to the questionnaire with their right hand using a joystick (Competition Pro USB, Speedlink, Weertzen, Germany) mounted in front of them. test

4.2.2.3 *Visual Stimuli*

Visual stimuli consisted of video clips presented for the entire movement duration. The camera that recorded the movies from a space-fixed position on the motion platform, recording either the mannequin or a red pillow (object) from above (i.e. a first person perspective - see Figure 4A-D). In the congruent conditions, participants saw the mannequin or the object in real time and left-

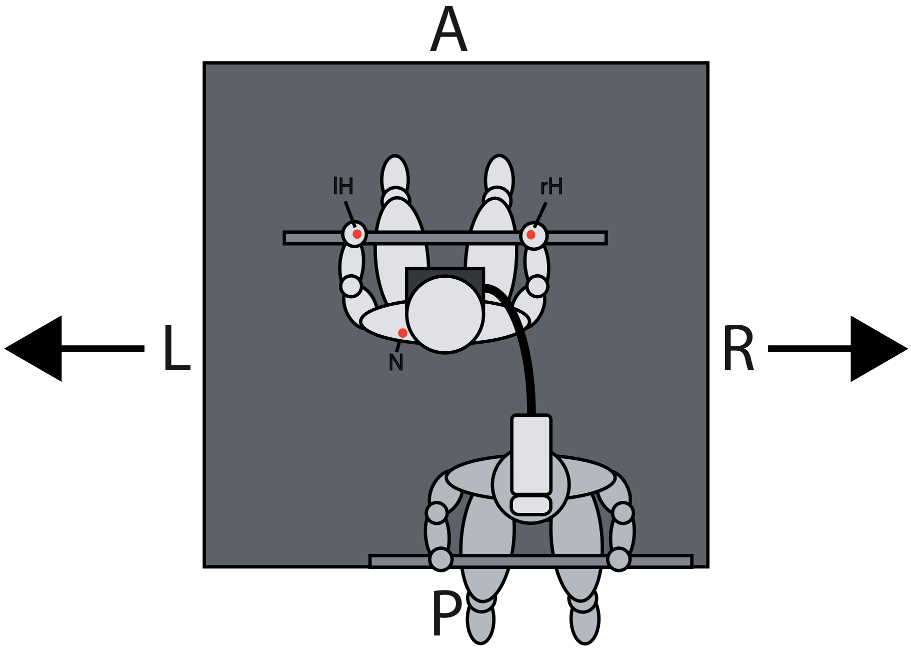

Figure 5: Scheme of the experimental set-up from an aerial view. The participant was seated in the middle of the motion platform (dark grey) and faced to the anterior part (A), wearing an HMD connected to a webcam and having attached three thermocouples (red dots, lH = left Hand, rH = right Hand, N = Neck). On the posterior part (P) of the platform a mannequin was positioned with a webcam above filming the movement. The motion platform was accelerated sinusoidally to the left (L) and to the right (R).

right mirrored by the presentation software. In this way, the seen movement corresponded to the felt movement. In the incongruent conditions, a temporal delay of one second was introduced by the software and additionally the video was not mirrored, thus, creating a temporal and spatial incongruence at the same time. In this way the participants saw the movement temporally delayed and in the direction opposite to how they experienced it. This incongruent condition was chosen based on pretests in order to increase the conflict between visual and vestibular cues.

4.2.3 *Measurement of the illusions*

4.2.3.1 *Questionnaire*

A questionnaire modified after Lenggenhager et al. (2007) and Petkova and Ehrsson (2008) was used in a German version to assess subjective aspects of the visuo-vestibular illusion (see Table 1 for an English translation of all items). Subjective ratings were recorded with a 30-steps visual analog scale using a joystick in which the left-most position represented 'very weak' and the right-most position 'very strong' The order of the questions was randomized over conditions and participants. An illusion score was calculated from the average of questions Q1, Q2 and Q4. Q2 was developed as an illusion question during pretests, as some participants spontaneously remarked the sensation of the feet floating in the air in the congruent mannequin condition despite the fact that the feet touched the platform. As in the seen video the mannequin and the object were floating, we thought that this question would be an interesting measure of visual capture of proprioception/touch and thus self-identification. In the traditional RHI literature, Q3 is usually considered a control question ("having two left/right hands"). However, in the present context of a vestibular induced FBI we do not consider it as a pure control question and thus report it separately. This decision was based on both clinical observations of multiple bodily consciousness (Brugger, Blanke, Regard, Bradford, & Landis, 2006) and corresponding experimental findings (Heydrich et al., 2013) and further reinforced by pilot experimentation. Q5 assessed the perceived match between the seen and the felt movement, while Q6 provided a measure for the perceived sickness during vestibular stimulation.

4.2.3.2 *Temperature*

Skin temperature was measured with a HH309A Data Logger Thermometer (Omega, Stamford, USA) following the procedure of Salomon et al. (2013). Two of the four thermocouples were placed on the dorsal part of the left and right hand, while one thermocouple was attached to the left side of the neck (over the sternocleidomastoid muscle). The fourth thermocouple was used to control room temperature and attached to the seat (see supplementary online material). Temperature was measured with a sampling rate of 0.5 Hz during each condition for the entire length of visuo-vestibular stimulation beginning six seconds before stimulation for establishing a baseline.

4.2.4 *Data preprocessing and analysis*

In one participant the temperature recording stopped due to technical issues and he was thus excluded from the temperature analysis. In another participant, the thermocouple attached to the neck fell off, therefore only hand temperature was included in the analysis.

In a first step, a temperature baseline was calculated for each participant by averaging three data points taken from the period of six seconds before movement initiation. To compute temperature changes over time, we calculated for each condition four periods from the 58 data points, averaging 14 (mean t1 and t2) or 15 (mean t3 and t4) data points respectively. T1 thus corresponded approximately to the first 30 seconds of stimulation, t2 to seconds 30 to 60, t3 to seconds 60 to 90, and t4 to seconds 90 to 120.

Moreover, temperature data from the left and right hands were averaged. Temperature changes were calculated by subtracting the baseline from the four averaged temperature data points (t1 to t4). To differentiate between illusion-induced temperature changes and unspecific changes over time, we subtracted

Table 1: Questions shown after the four conditions presented in a randomized order. Bold caption indicates the questions that formed the 'illusion score'.

Q1	**How strong was the feeling that the seen body/object was your own?**
Q2	**How strong was the feeling that your feet were hanging freely in the air?**
Q3	How strong was the feeling that you had two bodies?
Q4	**How strong was the feeling that you were detached from your own body?**
Q5	How much did the felt movement correspond to the seen movement?
Q6	How sick did you get?

for each averaged data point (t1 to t4) the mean over all four conditions (*congruent mannequin, incongruent mannequin, congruent object, incongruent object*) for that time point separately for the hand and the neck data.

4.2.5 *Statistical analysis*

Statistical analysis was performed using IBM SPSS Statistics 21 (IBM Corp., Armonk, NY, USA).

Questionnaires

For the questionnaire data three separate 2×2 repeated measures ANOVAs with within subject factors *body* (mannequin, object) and *congruence* (congruent, incongruent) were calculated for the illusion score (mean Q1, Q2, and Q4), for Q5, Q6, and for Q3. For these analyses, data from all 21 participants were used.

Skin temperature

To assess changes in skin temperature, a $2 \times 2 \times 4 \times 2$ repeated measures ANOVA with factors *body* (mannequin, object), *congruence* (congruent, incongruent), *time* (time point one to four) and *location* (hand, neck) was calculated. Significant interaction effects were analyzed with further ANOVAS. Pearson correlations were calculated between temperature and questionnaire scores for the significant effects.

4.3 RESULTS

4.3.1 *Questionnaire data*

The 2×2 ANOVA (within subject factors *body* and *congruence*) revealed a significant main effect of *body* for the illusion questions, $F_{1,20} = 4.39$, $P = .049$, $\eta^2 = .18$, showing that in the body conditions the illusion questions were rated higher (*mean difference* = 1.87, *SE* = .70). In addition, the ANOVA also revealed an interaction of *body* and *congruence*, $F_{1,20} = 4.87$, $P = .039$, $\eta^2 = .20$. Bonferroni corrected post hoc t tests revealed a significant difference for the illusion score between congruent mannequin and object condition (t_{20} = 2.58, P = .02), with the congruent mannequin condition being more illusory (*mean* = 9.83, *SD* = 5.16 versus object congruent mean = 7.29, *SD* = 5.48). There was no significant main effect of congruence (all F < .86, P > .72).

The ANOVA for Q3, the feeling of having two bodies, revealed a significant main effect of *body* for the illusion questions, $F_{1,\,20}$ = 6.42, P = .02, η^2 = .24, showing that in the body conditions the feeling of having two bodies was rated higher (*mean* difference = 2.10, *SE* = .83). There were no other significant main effects or interac-tions (all F < 2.14, P > .16).

The ANOVA for Q5, the perceived match between visual and vestibular signals, revealed a trend for the main effect of *congruence*, $F_{1,\,20}$ = 4.19, P = .054, η^2 = .17, i.e. the congruent conditions were rated as more congruent (*mean* difference = 2.43, *SE* = 1.19). No other main or interaction effects were significant (all F < .70, P > .41). The ANOVA for Q6, the sickness measure, revealed no significant main or interaction effects (all F < 2.47, P > .13).

4.3.2 *Skin temperature data*

In the repeated measures 2 × 2 × 4 × 2 ANOVA factors *body, congruence, time* and *location* there was a significant main effect of *congruence*, $F_{1,\,18}$ = 4.62, P < .05, η^2 = .20, meaning that temperature in the congruent conditions decreased more than in the incongruent conditions. For the interaction effect of *body* × *congruence* × *time* × location Mauchly's test indicated a violation of the assumption of sphericity, χ_{25} = 20.96 , P < .01. The degrees of freedom were therefore corrected using Huynh-Feldt estimates of sphericity (ϵ = .63) revealing a significant interaction effect of *body* × *congruence* × *time* × *location*, $F_{3,\,16}$ = 3.70, P = .04, η^2 = .17. Moreover, there was a trend for the interaction of *congruence* × *time*, $F_{3,\,16}$ = 2.80, P = .08, after degrees of freedom were corrected using Huynh-Feldt estimates of sphericity (ϵ = .59, Mauchly's test, χ_{25} = 20.96, P < .01). No other main effect or interaction was significant (F < 2.34, P > .13). Since the four-way interaction effect was significant, we calculated two sepa-

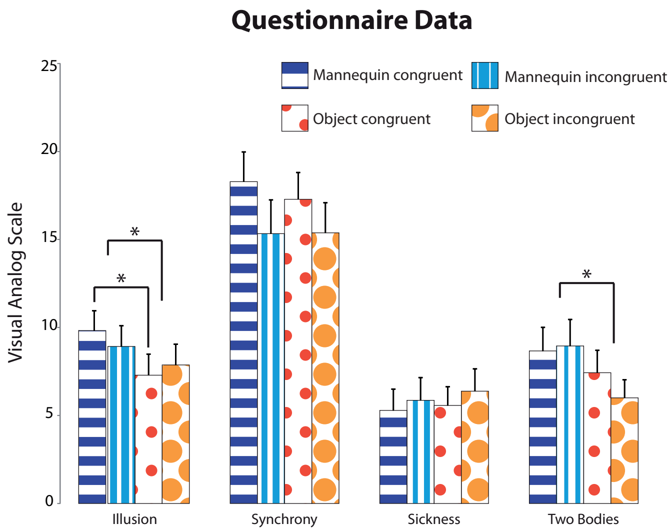

Figure 6: Questionnaire data. On the left, the averaged illusion scores on a visual analog scale (0 = disagree completely, 30 = agree completely) with the significant main effect of body (* = $P < 0.05$). In the middle, the values for the congruence judgment over all condition, with a trend for the main effect of delay. On the right the values for the sickness in each condition. Black lines show the standard error of the mean (SEM).

rate ANOVAs for each of the two anatomical locations (hand, neck) to explore the data in more detail.

The $2 \times 2 \times 4$ repeated measures ANOVA for the hands revealed a significant interaction effect of *body* $\times$ *congruence* $\times$ *time*, $F_{3,\,17} = 4.15$, $P = .04, \eta^2 = .18$ (see Figure 7, left panel), after degrees of freedom were corrected using Huynh-Feldt estimates of sphericity ($\epsilon = .51$, Mauchly's test, $\chi_{25} = 32.70$, $P < .01$; all other $F < 2.16$, $P > .16$).

Further ANOVAs for each time point for the hand revealed a significant main effect for *body* at time point one, $F_{1,\,19} = 4.56$, $P = .04, \eta^2 = .19$, (all other $F < 1.29$, $P > .27$). For time points 2 and 3, no significant main or interaction effect emerged (all $F < 2.33$, $P > .14$). The ANOVA at time point 4 showed an interaction effect of *body* $\times$ *congruence*, $F_{1,\,19} = 5.08$, $P = .04$, $\eta^2 = .21$ (see Figure 7, left panel). No main effect was significant (all $F < 1.77$, $P > .20$). The $2 \times 2 \times 4$ repeated measures ANOVA for the neck with factors *body, congruence* and *time* revealed only a trend for the main effect of *congruence* ($F_{1, 18}$ = 4.25, P = .054, η^2 = .19; all other F > 1.94, P > .16, see Figure 7, right panel).

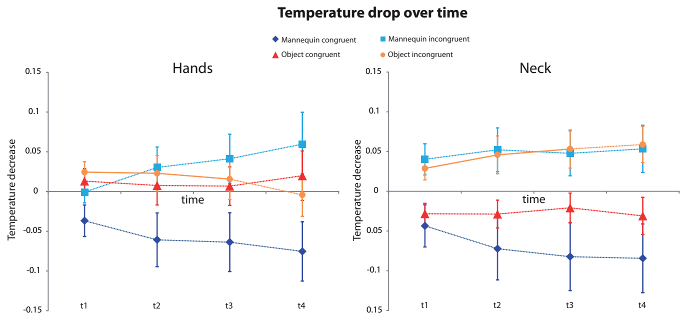

Figure 7: Changes of skin temperature in degree Celsius for the hands (left) and the neck (right) over time. Depicted are the four means for each condition (four different colors) and the SEM.

4.3.3 *Correlations*

Pearson product-moment correlations were calculated between the drop in temperature (mannequin congruent - mannequin incongruent at time point 4) and the illusion score as well as the scores to Q5 and Q3 (again congruent - incongruent). These analyses revealed no significant correlation (all P > .12).

4.4 DISCUSSION

The present study used a newly developed FBI setup to investigate how visuo-vestibular integration of bodily cues would modulate implicit and/or explicit illusory self-identification with another body (see reviews Blanke & Mohr, 2005; Lenggenhager et al., 2006; Lopez et al., 2008; Blanke, 2012; Pfeiffer et al., 2014). These were the two main findings:

First, the *implicit* measure proved sensitive to our manipulation, that is, we found a drop in skin temperature specifically during the illusion condition. This is in line with our hypothesis based on studies that manipulated visuo-tactile congruency in a similar context (Petkova & Ehrsson, 2008; Salomon et al., 2013). We thus argue that current models of body ownership (e.g. Petkova et al., 2011), which typically include visual, tactile and proprioceptive modalities only, would gain from including the vestibular system, especially if such a model addresses full body ownership (compare also Lenggenhager & Lopez, 2015; Lopez, 2013; Pfeiffer et al., 2014).

Second, in contrast to our hypothesis and to studies using conflicts between other sensory modalities, these implicit changes were not entirely reflected by explicit measures; the illusion scores were generally rather low and while the illusion was stronger in the congruent mannequin condition than in the congruent object condition, there was no difference between the congruent and the incongruent stimulation in the mannequin condition.

4.4.1 *Visuo-vestibular congruency induces a body-specific drop in temperature*

The temperature drop in the congruent mannequin condition indicates for the first time that a visuo-vestibular conflict might change the bodily self in predictable ways. Thermoregulation has been convincingly linked to altered ownership during similar full body and body part illusions through a modulation of the homeostatic activity (Moseley et al., 2008; Kammers et al., 2011; Salomon et al., 2013). Thermoregulation is prominently mediated by the insula (e.g. Diwadkar, Murphy, & Freedman, 2014), which generally plays a role in interoceptive signaling (Craig, 2002, 2009; Critchley, Wiens, Rotshtein, Ohman, & Dolan, 2004). Interestingly, tight neuroanatomical and functional links between vestibular and interoceptive systems based on shared representation in the insula have been demonstrated (see Balaban, 1999, for a review), making an influence of the vestibular system on thermoregulation plausible.

Our temperature data showed a main effect of congruency, i.e. a stronger temperature decrease during visuo-vestibular congruence than incongruence. Motion sickness, elicited by visuo-vestibular conflicts, has been linked to an altered thermoregulation (e.g. Hesse, 1874; Graybiel, 1969). However, the direction of temperature change is not conclusive (Holmes, King, Stott, & Clemes, 2002; Nobel, Eiken, Tribukait, Kolegard, & Mekjavic, 2006; Nobel, Tribukait, Mekjavic, & Eiken, 2012; Ngampramuan et al., 2014). Yet, motion sickness is unlikely to explain the temperature drop in our data as it did not differ between conditions, nor correlate with temperature alterations. Furthermore, the additionally significant interaction effect shows that the temperature drop was body-specific (i.e. stronger in the mannequin condition). This suggests that the temperature drop is not a pure interaction of multisensory conflict and thermoregulation, but importantly mediated by higher-level aspects of the bodily self, i.e. when the multisensory stimulation was coherent and also plausible from a top down perspective (seeing the body from a first person perspective) (compare Tsakiris & Haggard, 2005; Gallace, Soravia, Cattaneo, Moseley, & Vallar, 2014).

Remarkably we found this interaction effect for the hands, but not for the neck. Previous studies only measured skin temperature at anatomical locations that were visible during the experiment (Moseley et al., 2008; Salomon et al., 2013). Here, we used a thermocouple positioned at the neck of the participant, while the mannequin's neck was not seen (compare Figure 4 A and B). This might suggest that the thermoregulation was only affected for body parts, which were actually seen during the multisensory stimulation. Such hypothesis is in line with limb-specific modulation of skin temperature during vision of (Sadibolova & Longo, 2014) or attention to (Patrizi, 1912) certain body parts. Alternatively, hand-neck differences could be related to the physiological response pattern of body temperature regulation: body temperature drops first in the periphery to conserve the temperature of life-supporting central organs.

Generally, the size of the effects were comparable to the findings of a recent visuo-tactile FBI (Salomon et al., 2013), but much smaller than in the RHI (Moseley et al., 2008). This difference might either be linked to methodological issues (e.g. stimulation time, measuring device, sampling rate), to different functional and cortical mechanisms of full body as compared to body part representations (for an overview see Blanke, 2012) or to the novel combination of modalities manipulated in the present experiment (i.e. visuo-vestibular versus visuo-tactile integration in the previous experiments).

4.4.2 *Visuo-vestibular congruence marginally influences phenomenological aspects of the illusion*

Questionnaire data revealed a higher illusion score in the mannequin congruent as compared to the object congruent conditions, suggesting that self-identification with a mannequin is generally easier than with an object, most plausibly as a consequence of so-called top-down constraints (cp. Tsakiris & Haggard, 2005).

However, in contrast to comparable FBIs using congruence between other modalities (e.g. Petkova & Ehrsson, 2008), the illusion scores were rather low, and the congruency between visual and vestibular signal did not show the typical pattern of a stronger illusion in the congruent as compared to the incongruent condition. We suggest various plausible mechanisms underlying this "negative" result.

Visuo-vestibular congruence might be harder to be consciously detected than visuo-tactile congruence. While it is rarely explicitly assessed in classical RHI or FBI (compare also discussion in Suzuki et al., 2013), we can assume that participants are perfectly able to judge if a tactile and a visual event are presented congruently or not, at least in the range of the delays used in those studies. This was less evident for the visuo-vestibular congruency in our experimental setup, as shown by the mere trend for higher scores in the congruent as compared to the incongruent conditions in the "congruence question" (Q5). We suggest that the difficulty in judging congruence might be caused by a strong tendency to integrate visual and vestibular signals into one single percept. Studies on the perception of self-motion demonstrated that visual and vestibular inputs are generally integrated in a statistically optimal fashion, even when they are manipulated to generate conflicting signals. In these situations both, an overweighing of vestibular cues (Fetsch et al., 2010; Butler et al., 2011), as well a bias towards visual cues (Berger et al., 2010; Prsa et al., 2012), have been observed. Moreover, Ni and colleagues (2013) observed that gaze straight ahead dominates body straight ahead in determining the reference frame to define the perceived direction of motion, thus demonstrating that preference for vision-related variables extends also to the definition of space with respect to the self. The tendency to overweigh visual input fits with our participants' high congruence judgment, independent of the condition. Moreover, there seems to be an inability to weigh visuo-vestibular signals uncoupled, causing a mandatory fusion of visual and vestibular input (Prsa et al., 2012). This appears plausible as there is no distinct, conscious vestibular sense or percept (Angelaki & Cullen, 2008), and unlike other sensory stimulation, pure vestibular stimulation and sensation is very rare. In a nutshell, the vestibular system is intrinsically multisensory (Angelaki, Gu, & DeAngelis, 2009). This corroborates the lack of a spatially confined unimodal vestibular cortex (Guldin & Grusser, 1998) and with the fact that cortical vestibular centers are highly multimodal (e.g Buttner & Henn, 1976; Meng & Angelaki, 2010), for specific reviews see Blanke (2012) and Prsa and colleagues (2012).

Yet, even if the congruence was not consciously detected, it is still unclear, why it did only influence implicit but not explicit measures. Recent studies using cardio-visual conflict showed an explicit effect on body ownership both for the full body (Aspell et al., 2013) as well as for the rubber hand (Suzuki et al., 2013), even without the conscious differentiation of congruence and incongruence. Although implicit and explicit measurement were recorded at two different time points, we can rule out that the difference of temporal recording explains the lack of an effect or correlation between the two measures as previous studies had to deal with the same temporal issue, but managed to show a connection between the skin temperature and the questionnaire data (Moseley et al., 2008; Salomon et al., 2013).

Another reason why we did not find a modulation of congruence on the questionnaire data might be related to the fact that the illusion-related ratings were generally rather low. This could potentially be linked to methodological problems (i.e. the perspective on the body) or the choice of questions used to assess the illusion (note that the two typical referral-of-touch questions from Botvinick & Cohen (1998) were not adapted here). Alternatively and more interestingly, it could also be linked to the idea of stronger anchoring of the self through vestibular stimulation (Ferrè et al., 2014). The vestibular system -

similar to interoceptive signaling (see Tsakiris et al., 2011) - plays an important role in anchoring the self to the body (.e.g. Bonnier, 1905; Blanke et al., 2002; Blanke, 2004; Blanke et al., 2004; Blanke & Mohr, 2005; Blanke, 2012). It could thus be proposed that the additional veridical vestibular stimulation during our experimental conditions has increased the anchoring of the self to the body and thus decreased the FBI. Further experiments will be necessary to test this hypothesis.

4.4.3 *Limitations and Outlook*

The visuo-vestibular congruence was barely detected consciously by the participants in our experimental setup. Next to the strong tendency of the brain to integrate visuo-vestibular signals described above, this may have resulted from the fact that we have only used translational interaural accelerations, as well as from the fact that the vestibular and the visual stimulation were only phase-shifted and spatially mirrored, but were along the same axis. Future studies might consider using different kinds of vestibular stimulations, which possibly elicit a stronger conflict between the visual and the vestibular modalities, yet it is important to avoid severe motion sickness. A variation of stimulation duration could further control for effects of adaptation to the visuo-vestibular conflict. Adding three-dimensional images to the seen video might make the seen motion more realistic, even more as recent finding that optimal visuo-vestibular cue integration is highly dependent on stereoscopic visual input (Butler et al., 2011).

The skin temperature drop as physiological correlate of ownership has recently been doubted on the grounds of a lack of replication of the data (Rohde, Wold, Karnath, & Ernst, 2013). These authors have shown that decreases in ownership are not always accompanied by corresponding decreases in skin temperature and argue that the temperature drop might rather reflect changes in arousal or social contact during the tactile stimulation in the RHI (e.g. Moseley et al., 2008). Additionally, they showed a dissociation between the cooling of the hand and the subjectively reported ownership over the hand, which fits nicely also to our findings. Thereby, we believe that our experiment might contribute to the discussion started by Rohde et al. (2013): While we cannot completely rule out the effect of arousal, using vestibular input delivered by a motion platform, we show that social contact is not mandatory to induce the cooling effect, corroborated by Salomon et al., (2013) who used a robot for tactile stimulation. Those inconsistencies but also similarities encourage further research to understand the cause of cooling in bodily illusions better.

4.4.4 *Conclusion*

Results of the present experiment suggest that vestibular mechanisms importantly influence multisensory integration underlying the bodily self even if we might not be consciously aware of it.

4.5 ACKNOWLEDGMENT

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5 STUDY2: WHEN LESS IS MORE - IMPLICIT PREFERENCE FOR INCOMPLETE BODIES IN XENOMELIA

ABSTRACT

Individuals with xenomelia identify with an amputated rather than with their physically complete, healthy body. They often mimic amputees and show a strong admiration of and sexual attraction towards them. Here we investigated for the first time empirically whether such unusual preference for amputated bodies is present also on an implicit level. Using the well-validated Implicit Association Test we show that individuals with xenomelia manifested a stronger implicit and explicit preference for amputated bodies than a normally-limbed control group and a group of involuntary amputees did. Interestingly, the two latter groups did not differ in their implicit and explicit preference for complete versus amputated bodies. These findings are an important step in understanding how deeply rooted attitudes about a socially normative body appearance may be influenced by a developmentally disordered experience of one's own bodily self. We conclude that this is the first behavioral evidence demonstrating a conflict of self-identification on an implicit level and this enriches current understandings of xenomelia as a primarily neurological disorder.

5.1 INTRODUCTION

The experience that we own our body is often taken for granted. Yet, the unity of body and self is surprisingly vulnerable (Brugger & Lenggenhager, 2014). A case in point is Body Integrity Identity Disorder (BIID) (First, 2005), also described as xenomelia ("foreign limb syndrome") (McGeoch et al., 2011), a condition which currently captures the attention of the popular media

(Ananthaswamy, 2015) and that of scientific representatives (Ramachandran et al., 2009) and medical ethics (Ryan, 2008) alike.

Individuals with xenomelia experience their body as disturbingly "overcomplete": they feel that their true identity is that of an amputee and accordingly demand the right of elective limb amputation (Ryan, 2008). While previous research focused on xenomelia as a neurological condition in the narrow sense (Hilti et al., 2013; McGeoch et al., 2011), several associated signs point to significant social co-determinants (Brugger et al., 2013; Brugger & Lenggenhager, 2014). First, the desire for amputation is often triggered by encounters with amputees (Aoyama, Krummenacher, Palla, Hilti, & Brugger, 2012). Second, a profound admiration for amputees up to a sexual attraction towards incomplete bodies has been described in some individuals with xenomelia (De Preester, 2013; First, 2005) and third, affected persons frequently pretend in private or public to be amputees. The perception of one's own and another person's body are intimately linked (Schilder, 1935), and sensorimotor processes are influenced by observation and imitation of others (de Guzman, Bird, Banissy, & Catmur, 2016; Tsakiris, 2016). Such shared neural mechanisms are modulated by interpersonal relations (Désy & Théoret, 2007), generally suggesting that the stronger they are, the more similar and positive another person is explicitly but also implicitly perceived and vice versa (Maister, Sebanz, Knoblich, & Tsakiris, 2013). While an overt behavioral preference for having an amputated body is a core aspect of xenomelia, it is unknown whether positive attitudes towards amputated bodies are also represented on a more implicit level. Here, we recruited individuals with xenomelia and two age- and sex-matched groups of normally-limbed controls and involuntary limb amputees to investigate their implicit preference for an amputated body, as measured with a web based implicit association test (IAT) (Greenwald et al., 1998). We hypothesized that individuals with xenomelia compared to normally-limbed persons would show a stronger explicit preference for amputated bodies. More importantly, we predicted that unlike the normally-limbed controls, they would also show an implicit preference for amputated bodies. Similarly, Olson and colleagues (2015) found in children with Gender Dysphoria, a condition with which xenomelia shares several key features (First, 2005), that their explicit preferences for the expressed gender is also reflected in an implicit preference as measured by the IAT. For the comparison of individuals with xenomelia and the amputees, the available literature was not sufficient to develop directed hypotheses for the explicit and implicit preferences.

5.2 METHODS

5.2.1 *Participants*

Participants with xenomelia were recruited over dedicated internet platforms and organizations and were thus self-designated individuals with xenomelia. Other psychiatric conditions could not strictly be excluded. Age- and sex-matched control participants with an amputation were recruited using the database created for a previous comprehensive study about body representation in amputees (Bekrater-Bodmann et al., 2015).

Our original sample of individuals with xenomelia consisted of 45 participants. However, to reduce heterogeneity, we excluded nine individuals who already underwent an amputation. Moreover, we excluded two further participants who desired not amputation, but paralysis. Thirty-four individuals with self-declared amputation desire for one or both legs, 35 lower-limb amputees, and 35 normally-limbed controls were finally included in the study. Most involuntary amputees underwent an amputation after traffic or work accidents. A Bayesian ANOVA revealed weak evidence for no age differences between the three groups (BF_{01} = 2.58) in comparison to a model including an age effect. A detailed description of the participants is listed in table 2.

The study was approved by the Cantonal Ethics Committee of Zurich and conducted according to the ethical standards of the Declaration of Helsinki.

Table 2: Descriptives of the participants

	Age	Sex	Afflicted lower limb	Duration of Amputation desire Time since amputation	ZXS Pure Amputation	ZXS Erotic Attraction	ZXS Pretending Behavior	Subjective probability of amputation
Xenomelia	45.32 (±11.52)	Male = 32	Left = 19	35.88 (±14.38)	5.33 (±0.90)	4.64 (±1.01)	3.84 (±1.01)	8.18 (±4.62)
	Range = 28 - 77	Female = 2	Right = 8	Range = 6 - 67	Range = 2.5 - 6	Range = 2.75 - 6	Range = 1.5 – 5.25	Range = 2 – 16
			Both = 7					
Amputees	50.97 (±9.11)	Male = 32	Left = 23	23.74 (±11.38)	-	-	-	-
	Range = 31 - 84	Female = 3	Right = 11	Range = 2 - 44				
			Both = 1					
Normally-limbed	46.26 (±17.47)	Male = 30	-	-	-	-	-	-
	Range = 21 - 72	Female = 5						

5.2.2 *General procedure*

Participants were asked to perform the experiment online on a computer with a keyboard and a mouse in a calm moment without any disturbances, and in one session. The full experiment included the IAT, the explicit questions targeting body preference, some group-specific questions and the Body Image Task (Fuentes, Pazzaglia, Longo, Scivoletto, & Haggard, 2013; Fuentes, Longo, & Haggard, 2013). The latter is not reported here, as the number of participants was too low (only 14 individuals with xenomelia completed the task) and an analysis of the data would not have allowed any reasonable interpretation. All testing took about thirty minutes.

5.2.3 *IAT*

To measure the participants' strength of automatic association between the concepts of a 'complete' or 'amputated body' and its positive and negative valence, we modified an existing open source and JavaScript based IAT (`https://github.com/winteram/IAT`). The IAT consisted of 20 drawn pictures of normally-limbed people (concept of complete body) or people with one missing leg (concept of amputated body) paired with words associated with positive (e.g. love, peaceful) or negative (e.g. war, horrible) concepts (for a more detailed description see Fig. 8 and its legend). The participants' bias towards an incomplete or complete body was measured by the response time and accuracy of categorizing the pictures with a positive concept relative to a negative concept. The IAT consisted of seven blocks (Greenwald, Nosek, & Banaji, 2003). All stimuli were displayed in the middle of a central white rectangle with the dimensions of 540×540 pixels (Fig. 9a). The stimulus remained on the screen until a response was given. Each block started with detailed instructions. Participants were instructed to respond as fast and accurately as possible with the keys 'e' and 'i' on the keyboard. After an incorrect response a red 'X' popped up immediately. An incorrect response was defined as the misclassification of a picture or a word. Responses longer than 10 seconds were excluded and latencies of incorrect responses were replaced with the block mean and added a penalty of 600 ms, according to the improved algorithm to calculate the IAT value proposed by Greenwald and colleagues (2003). The IAT value was calculated with the improved scoring algorithm: The mean difference in reaction time between the incongruent and congruent blocks was divided by the pooled standard deviation (SD) of all correct trials so that positive IAT scores indicate an implicit preference for complete bodies and negative IAT scores indicate an implicit preference for amputated bodies.

5.2.4 *Explicit attitude*

Participants were also asked to rate the valence of the concepts of 'complete bodies' and 'amputated bodies' on a rating scale from 0 to 20. The difference between these two ratings was computed and normalized so that it ranged from -1 (maximally positive attitude towards amputated bodies, accordingly, and maximally negative attitude towards complete bodies) to 1 (maximally negative attitude towards amputated bodies and, accordingly, maximally positive attitude towards complete bodies). One amputee did not rate the valence of "complete body" and his normalized difference value was thus excluded from further analyses.

5.2.5 *Group specific questions*

To quantify core aspects of xenomelia, we adopted an online version of the Zurich Xenomelia Scale (ZXS) for the recruited xenomelia group. The ZXS is a questionnaire that quantifies three essential aspects of xenomelia ('pure amputation desire', 'erotic attraction' and 'pretending behavior') on a scale from 1 to 6 and is described in more detail elsewhere (Aoyama et al., 2012).

They were also asked to indicate which limb(s) their amputation desire is directed to. Moreover, they were asked whether they already underwent an amputation and to indicate their age when first becoming aware of the desire.

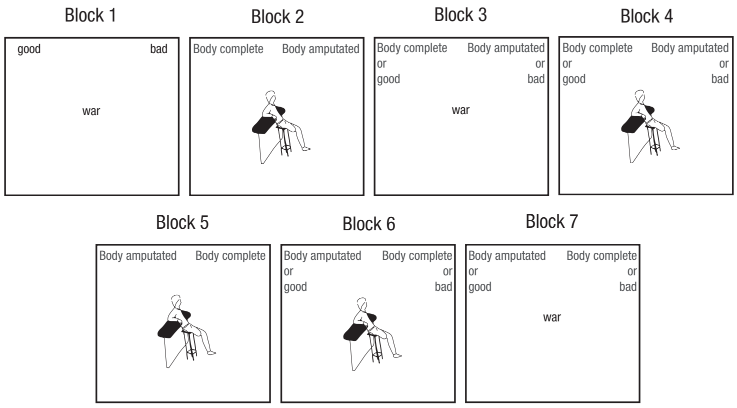

Figure 8: A depiction of the seven blocks of the adapted online IAT. In the first two blocks, pictures and words were presented separately each 20 times and had to be classified as either positive/negative (words) or amputated/complete body (pictures) with the keys 'e' for positive and 'i' for negative concepts in block one and similarly in block one with the keys 'e' for complete bodies and 'i' for amputated bodies. In blocks three and four, the concepts of complete bodies and positive words, respectively were presented on the left (key 'e' had to be pressed) while amputated bodies or negative words were shown on the right (key 'i' had to be pressed). Block three and four consisted of 80 trials in total. In these blocks, the association strength between the concepts 'good' and 'body complete'/'bad' and 'body amputated' were measured. In block five, pictures had to be categorized but with the response to complete (right, key 'i') and amputated bodies (left, key 'e') switched. In blocks six and seven, amputated bodies or positive words were presented on the left side (key 'e'), while complete bodies or negative words were presented on the right (key 'i'). Those last two blocks consisted of 80 trials in total as well. In these blocks the association strength between the concepts 'bad' and 'body complete'/'good' and 'body amputated' were measured.

They were also asked to assess the subjective probability of an amputation of the undesired limb within a year on a scale from 0 to 20.

Amputees were asked how strongly they experienced a phantom of their amputated limb on a numerical rating scale from 0 (no phantom) to 20 (very strong), how strong their phantom pain was from 0 (no phantom pain) to 20 (very strong), and how often they used a prosthesis from 0 (never) to 20 (very often). Those values were used for further explorative correlational analyses.

5.2.6 *Body representation in dreams*

Based on previous reviews and finding regarding recalled body representation in dreams in amputees (Brugger, 2008; Bekrater-Bodmann et al., 2015), participants were asked to rate how often they recalled their body during dreams as complete or incomplete on a numerical rating scale from 0 (never) to 20 (always). The difference between these two ratings was computed and normalized so that it ranged from -1 (very often incomplete and never complete) to 1 (very often complete and never incomplete). Those normalized values were used for further explorative correlational analyses.

5.2.7 *Statistical analysis*

All statistical analyses were performed using the statistical language R (R Core Team, 2016). A Bayesian data analysis approach was chosen as it allows expressing statistical evidence for a defined compared to a null hypothesis using BFs (the ratio of the data's likelihood given two competing hypotheses) (Rouder, Speckman, Sun, Morey, & Iverson, 2009). For group comparisons, two-sampled Bayesian Jeffreys-Zellner-Siow (JZS) t-tests with default-scaled Cauchy priors ($r = .707$) were calculated using the BayesFactor package for R (Morey & Rouder, 2015). The null model is defined as no difference between two groups. According to Jeffreys (1961), a BF above 3 yields substantial evidence for one of the two defined models, in our case for the null model. A BF below 1/3 provides substantial evidence for the alternative model. The credible interval (CI) is defined as 95% interval of the posterior density of the effect size parameter δ.

For further correlational explorative analyses, correlation coefficients and BFs were calculated for undirected correlations using JASP (Love et al., 2015) and a beta prior width of 1. The posterior distributions of the most interesting correlations were described in more detail using the BayesMed package implemented in R (Nuijten, Wetzels, Matzke, Dolan, & Wagenmakers, 2015). This package provides functions for default Bayesian hypothesis tests for correlations using a JZS prior set-up. The posterior distributions were obtained from 10,000 Monte Carlo Markov Chain iterations and 1,000 burn-in iterations discarded at the beginning.

5.3 RESULTS

5.3.1 *IAT*

Results of the IAT are shown in Figure 9C. Data analysis (see SOM for additional correlations and an analogous analysis using null hypothesis testing) suggests weak evidence (BF_{01} = .74, credible interval (CI) for δ = [-.66, -.0005]) for an implicit preference for the amputated body in the xenomelia group (IAT score mean = - 0.18), whereas both amputees (IAT mean = .85, BF_{01} = 2.85 * 10^{-10}, CI for δ = [1.21, 2.28]) and the normally-limbed controls (IAT mean = .86, BF_{01} = 3.82 * 10^{-13}, CI for δ = [1.62, 2.89]) show a strong implicit preference for the complete body. Two sampled Bayesian t-tests of the IAT score revealed a relatively stronger preference towards amputated bodies in the xenomelia group as compared to both the amputees (BF_{01} = 1.06 * 10^{-10}, CI for δ = [-2.69, -1.46]) and the normally-limbed controls (BF_{01} = 1.60 * 10^{-12}, CI for δ = [-2.96, -1.70]). There is substantial evidence for the model assuming no difference in the latter two groups' implicit preferences (BF_{01} = 4.05, CI for δ = [-.43, .43]).

5.3.2 *Explicit Values*

Data analysis for the explicit preferences shows strong evidence (BF_{01} = 1.03 * 10^{-12}, CI for δ = [-2.95, -1.61]) for an explicit preference for the amputated body in the xenomelia group (mean = - .72) (Fig. 9B), whereas both amputees (mean = .65, BF_{01} = 9.85 * 10^{-11}, CI for δ = [1.30, 2.48]) and the normally-limbed controls (mean = .66, BF_{01} = 2.06 * 10^{-8}, CI for δ = [.96, 1.94]) show a strong explicit preference for the complete body (see Figure 9D). The xenomelia group preferred the amputated body more than the amputees (BF_{01} = 1.39 * 10^{-23}, CI for δ = [-4.9, -3.28]) and the normally-limbed controls (BF_{01} = 1.82 * 10^{-20}, CI for

δ = [-4.31, -2.82]), while for the two latter groups there is substantial evidence for the model postulating no difference (BF_{01} = 4.03, CI for δ = [-.43, .42]).

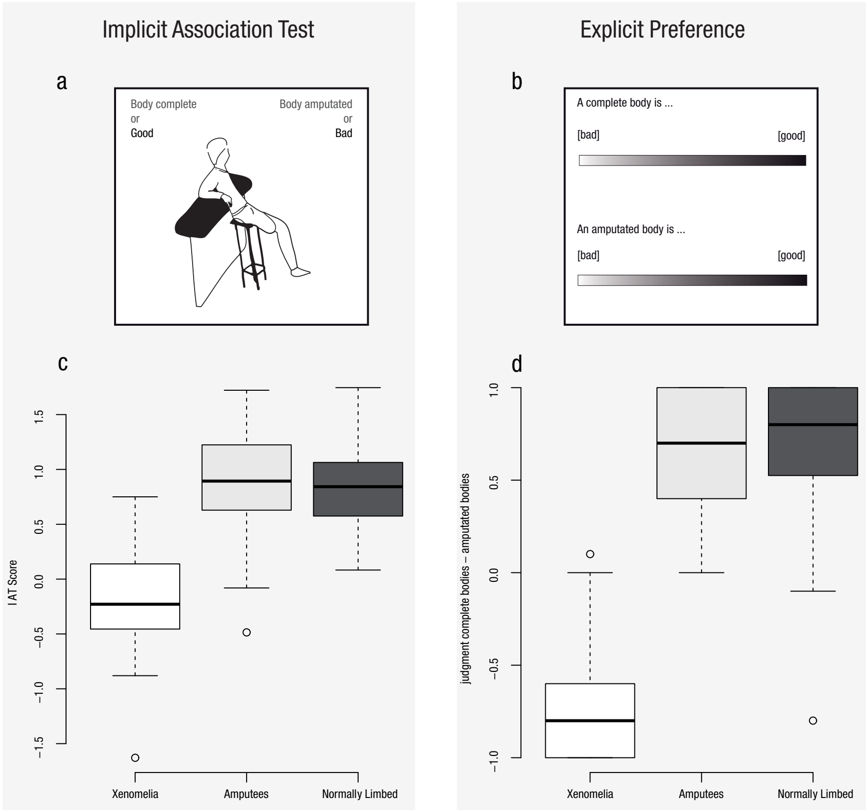

Figure 9: Illustration of methods (upper panel) and results (lower panel) for the implicit measure of preferences (left) and for the explicit measure of preference (right). (a) A sample picture of an amputated body presented in the IAT to evaluate the implicit attitude towards complete and amputated bodies. (b) The two Visual Analog Scales used to measure the explicit attitudes towards complete and amputated bodies. (c) The IAT scores in the three tested groups as boxplots; positive values represent an implicit preference for complete bodies over amputated bodies. (d) The normalized differences of the explicit attitudes as boxplots; positive values represent an explicit preference for complete bodies.

5.3.3 *Correlations*

Explorative correlations are shown in Supplementary Tables 1-3. Using the JSZ prior set-up implemented in the BayesMed package, the posterior distribution of the correlation coefficient for the duration of amputation desire and the body representation in dreams in the xenomelia group yielded a mean correlation of -.47 with a CI ranging from -.83 to -.10 and posterior probability of a correlation of .78. Likewise, the posterior distribution of the correlation coefficient for the relative explicit preference and the pure amputation score in the ZXS in the xenomelia group showed a mean correlation of -.48 with a CI ranging from -.78 to -.17 and posterior probability of a correlation of .92. In the amputees, there was a positive correlation between phantom pain strength and the IAT score with a mean correlation coefficient of .49, a CI ranging from 0.19 to .78 and a posterior probability of a correlation of .94.

5.4 DISCUSSION

The present study investigated explicit and, more importantly, implicit attitudes towards complete and amputated bodies in individuals suffering from xenomelia, involuntary amputees, and normally-limbed controls. It is thus the first study directly comparing a rather large and homogenous sample of individuals with xenomelia with participants actually suffering from amputation, with both groups having their lower limbs affected.

While amputees and normally-limbed controls showed strong implicit and explicit preferences for complete bodies, which is in line with people's general attitude towards disabled individuals (e.g. Wilson & Scior, 2014), the IAT scores from individuals with xenomelia differed strongly. The latter group showed a strong explicit and a weak implicit preference for amputated bodies. This is the first behavioral evidence for a conflict of self-identification in xenomelia on an implicit level, as affected individuals appear to prefer the bodily state of an out-group that does not physically match its membership criteria. Plausibly, the identification with or attraction towards amputees was strong enough to overcome negative biases and connotations typically associated with amputees. Yet, from the current results it is not possible to deduce whether there is a causal relationship between the implicit preference for impaired bodies and the persistent mimicking of the amputees' behavior. Blurred self-other-boundaries induced through own-body related multisensory conflicts have shown to influence implicit attitudes (Maister et al., 2015) and vice versa (Bufalari, Lenggenhager, Porciello, Serra Holmes, & Aglioti, 2014), indicating that an altered representation of the body might contribute to the present effects. The weak preference for amputated bodies is even more remarkable, when considering that the involuntary amputees showed the same negative bias towards amputees as the normally-limbed controls did. This finding is in line with recent evidence from spinal cord injury patients, who continue to show negative implicit attitudes towards their own in-group despite a change in explicit preference (Galli, Lenggenhager, Scivoletto, Molinari, & Pazzaglia, 2015). The positive correlation between the IAT score and phantom pain but not phantom sensations experienced by the amputees in the present sample (see SOM for the explorative correlations), could suggest that pain keeps the negative connotations upright. Interestingly, explicit and implicit preferences in our study were unrelated in all three groups. Corresponding to this dissociation, the pure amputation subscale of the ZXS was associated with explicit but not implicit body preferences. Similarly, a literature review on attitudes towards individuals with disabilities concluded that there is weak to no association between explicit and implicit measures (Wilson & Scior, 2014). A low correspondence between explicit and implicit measures has been shown to be associated with four factors (Nosek, 2005): a) self-representation, which describes the modification of an explicit preference for personal or social reasons, b) evaluative strength, which predicts higher associations for personally important and frequently emerging contexts, c) dimensionality, with unipolar categories causing lower associations compared to bipolar ones, and d) distinctiveness, which characterizes the perceived incongruence between one's own and societal norms. We can only speculate about which factor might have driven the missing relationship between implicit and explicit measures in the present study. However, since all groups show this missing association to a comparable degree, it is likely that the dimensionality behind preferences for intact and amputated bodies is rather unipolar than bipolar, indicating that an individual with xenomelia could prefer amputated bodies while simultaneously not rejecting intact bodies. Furthermore, considering the duration of the desire in the xenomelia group (in our sample on average more than 35 years), it is likely that higher-order cognitions based on long-lasting experiences overbuild and shape explicit measures.

The fact that the individuals with xenomelia behave strikingly different from normally limbed controls and amputees, stresses the importance of considering social factors in current scientific models of xenomelia. A similar implicit preference for the desired rather than the physical body state has only recently been shown empirically in children with Gender Dysphoria (Olson et al., 2015), a condition clinically related to xenomelia, but socially more generally sanctioned. Our findings corroborate the importance of implicit measures towards body states in conditions of a mismatch between physical realization and desired ideal of one's body. The comparison between individuals with xenomelia and participants suffering from an involuntary amputation provides insights into the relation between one's physical body and an internally stored body model. Amputees showed a remarkably preserved preference for intact bodies, even decades after amputation. This finding is confirmed by a missing relationship between time since amputation and implicit attitude towards the intactness of a body, as it indicates that the perception and evaluation of physical attributes in in- and outgroups might be relatively stable. For social evaluation, amputees might draw back on an internally stored body model, which finds perceptual expression in the fact that more than 80% of limb amputees report phantom limb awareness (Giummarra et al., 2010). In contrast and while physically intact, individuals suffering from xenomelia report perceived foreignness for the affected body part (Hilti et al., 2013). If the present results rely on a stored body model independent of the physical body, the implicit preference for amputated bodies in xenomelia might be opposite to what is observed in amputees. The desire for amputation as well as pretending behavior in xenomelia might not only reflect the need to feel physically 'intact', but also to belong to a group that is more similar to one's individual body representation. Prospective studies have to investigate how exactly an internally stored body model may shape social cognition.

5.4.1 *Limitations and Outlook*

The web-based nature of the study allows to collect data of a number of participants that would be unthinkable in a lab environment. At the same time, this procedure is accompanied by some disadvantages: The participation of the study is based on the self-diagnosis of xenomelia. Although we have control measurements such as the ZXS and the precise description of the demarcation line on the unwanted limb that favor the assumption of the participants' authenticity, there was no personal interview with detailed questions. We may add, however, that there are currently no established clinical diagnostic guidelines for diagnosing xenomelia.

The explicit measure we used relies entirely on two visual analog scales and its validity is thus barely comparable to the well-validated and reliable IAT. Because of their reliability, implicit measures such as the IAT offer an interesting addition to the future assessment of xenomelia, maybe even in a clinical context. At the same time, comparable explicit measures have to be developed further.

Individuals with xenomelia often report a very early onset of their desire. Thus, even more insight into the cognitive patterns of xenomelia could be gained from a comparison with individuals with congenital absence of a limb as it might sketch out developmental aspects of xenomelia (Hilti & Brugger, 2010). Such a comparison may elucidate some basic questions of both physical and representational integrity.

As the current study solely focused on the implicit attitude towards amputated bodies, the underlying neural mechanisms of such cognitive processes are still unknown. Neural correlates of the IAT (see e.g. Schiller et al., 2016) are of high interest as they would offer a more direct insight into the interaction of neurological and social aspects of xenomelia.

5.5 Acknowledgment

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5.6 Author contributions

BL and PB developed the study concept. BL, GM and PB contributed to the study design. Participant recruitment and data collection were performed by BL, GM and RBB. GM performed the data analysis and interpretation under the supervision of all other authors. All authors wrote the manuscript and approved the final version for submission.

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Study 3: Reducing Pain by Moving? A Commentary to Ferrè et al. (2013)

Strong connections and mutual interactions between the vestibular and nociceptive systems are reflected in an early and widely use of devices for vestibular stimulation (e.g. hanging beds) to alleviate pain (Grabherr et al., 2015). Corroboratory, clinical evidence suggested artificial vestibular stimulation successful in temporarily relieving various symptoms of neuropathic pain (André, Martinet, Paysant, Beis, & Le Chapelain, 2001; McGeoch et al., 2009). Yet, only recently, a direct beneficial influence of artificial vestibular stimulation on pain was experimentally demonstrated in healthy participants (Ferrè et al., 2013). These authors used a strong, unilateral vestibular stimulation induced by irrigating iced water into the left ear. This non-physiological stimulus activates the peripheral vestibular system and induces strong illusory self-motion and often vertigo (Lopez & Blanke, 2014) and, according to this recent study, reduces sensitivity to heat pain.

Inspired by this highly relevant finding, we set out to test whether a similar analgesic effect could be induced by natural vestibular stimulation (i.e. by head/body motion on a chair) contrasting the previously used artificial vestibular stimulation. There are several important physiological differences between the different vestibular stimulation techniques (see Palla & Lenggenhager, 2014), and, in view of a potential therapeutic use, it is central to understand what aspects of the stimulation could contribute to its analgesic effects. Hence, we intended to extend and complement their findings by investigating the influence of natural vestibular stimulation on heat pain detection thresholds (see SOM for additional sensory detection thresholds neurophysiological measures). In order to test whether effects truly relate to the vestibular stimulation or to the sensation/illusion of moving in general, we included visual optokinetic stimulation (i.e. coherently moving dots to induce illusory self-motion in the opposite direction (vection Brandt et al., 1973). A visual stimuli with incoherently moving random dots that does not induce illusory self-motion was used as further control condition. Since a direct interaction between vestibular and nociceptive input has been suggested (Ferrè et al., 2013, 2015), we expected natural vestibular stimulation to increase heat pain thresholds. If the feeling of moving through space rather than the vestibular stimulation itself reduces pain (Lenggenhager & Lopez, 2015), a similar effect could be expected for the optokinetic stimulations. No increase of pain thresholds was expected for the random dots condition.

Twenty healthy, right-handed men participated (mean age 31.1 +- 9.37, range 20 - 54) and provided written informed consent before participating in this study that had been approved by the local ethic committee and was conducted in accordance with the Declaration of Helsinki. Participants underwent two experimental blocks in counter-balanced order, one assessing "subjective" threshold measures (comparable to the method used by Ferrè et al., 2013, see below) and one assessing "objective" heat pain evoked potentials (see SOM)).

In the "subjective block", heat pain thresholds (HPT) were assessed at the dorsum of the left hand using the quantitative sensory testing (QST) method (temperature slope, 1°C/s; baseline temperature, 32°C (Maier et al., 2010) with the TSA 2001-II device (MEDOC, Ramat Yishai, Israel). The left hand was chosen in all conditions, as right hemispheric dominance in right-handed participants has been shown for vestibular processes (Dieterich et al., 2003). As in Ferrè et al. (2013), a baseline measure was always taken first. The vestibular and the visual stimulation mini-blocks were counterbalanced and each included three conditions presented again in counterbalanced order (cp. Figure 10A).

For the vestibular stimulation, participants were seated in complete darkness upright and head restrained on a 3D-turntable (Acutronic, Switzerland). Three frequencies of sinusoidal yaw oscillation were used: 0.1, 0.3 and 0.7 Hz. The peak angular velocity, the relevant stimuli for the vestibular system, was 30 deg/s at all frequencies and, consequently, the chair sinusoidally oscillated

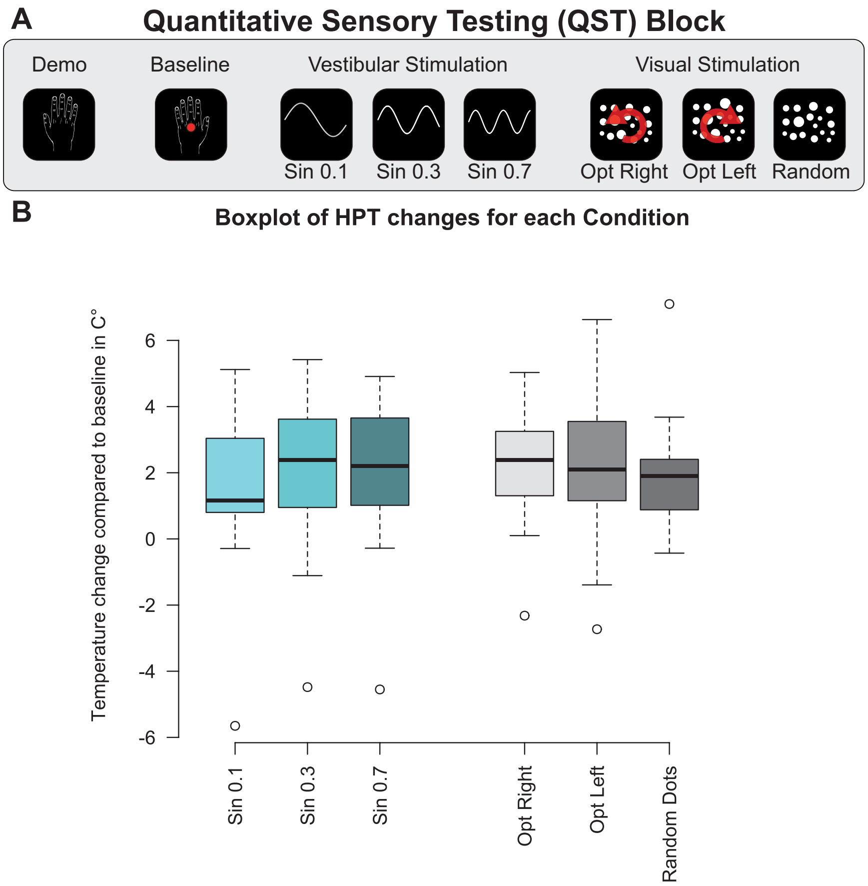

Figure 10: Experimental design and main result. A) Experimental Set-Up. Participants always underwent a baseline measurement for the quantitative sensory testing (QST) first. The order of the vestibular and visual stimulation mini-blocks was counterbalanced and the conditions within those mini-blocks were counterbalanced as well. The red arrow corresponds to the real or illusory motion direction, respectively. B) Changes in the heat pain thresholds (HPTs) compared baseline presented in box plots. While, all conditions lead to increased HPT compared to the baseline, a repeated measures ANOVA revealed no effect of condition (see text for more details).

between -47° to +47° at 0.1 Hz, between +/-16° at 0.3 Hz and between +/-7° at 0.7 Hz.

Full-field visual stimulation on a head mounted display (Oculus Rift, Oculus, Irvine, USA) was used. White dots were moving at a constant velocity either coherently to the left, coherently to the right or randomly to all directions.

The results of the stimulation related changes in HPT with respect to the baseline measure are depicted in Figure 10B. While one sample t-tests revealed that all stimulation conditions were different than baseline (all $p < 0.005$, Bonferroni corrected alpha = 0.008), a repeated measures one way ANOVA suggested no difference between the effect of the six different stimulation conditions ($F_{2.92,\ 55.51} = .88$, $p = .45$). As classical null hypothesis testing is not equipped to draw conclusions from non-significant results (Dienes, 2014), we additionally calculated a Bayes Factor (BF) for a repeated measures ANOVA model with factor condition (six levels) with the BayesFactor package (Rouder, Morey, Speckman, & Province, 2012) for the statistical programming language R (R Core Team, 2016). The results confirmed the strong evidence in favor of the null model (no difference between stimulation) with a BF of 11.11 ($BF_{\text{Null Model}}/BF_{\text{condition}}$). The average increase over baseline in our study (mean 1.96°C) was exactly the same to the one found by Ferrè et al. (2013, 1.96°C).

In conclusion, our data suggest that while all vestibular and visual stimulations significantly increase heat pain thresholds as compared to baseline, they do not differ from each other. The fact that even the random dots stimulation, which should not activate the vestibular system, increases the pain threshold by about the same amount as actual vestibular stimulation, suggests however, to our opinion, rather non-specific effects causing the general decrease in heat pain sensitivity, plausibly linked to distraction (Bantick et al., 2002). Ferrè and co-authors (2013) excluded such non-specific effects as an interpretation of their data (a) as the thresholds were modulated in the opposite direction for pain and tactile detection thresholds (Ferrè et al., 2013), (b) as they remained stable after the CVS (Ferrè et al., 2013), while attentional effects should decrease and (c) as they found an early modulation of pain evoked potentials (Ferrè et al., 2015). In their study the threshold was measured post-CVS, thus when there was no actual stimulation, nor any subjective (e.g. vertigo) or objective (nystagmus) signs of the vestibular stimulation. Nevertheless, Ferrè and colleagues (2013) argue that CVS is known to last for several minutes after the end of stimulation. The fact that we did not find any specific effect of stimulation could originate from the difference in the methods used, which are likely to activate slightly different cortical networks (Lopez et al., 2012). Yet, due to movement constraints in the fMRI, the network involved in natural vestibular stimulation remains largely unknown. Furthermore, in view that ice-water is a very strong vestibular stimulus; one could argue that the vestibular stimulation used in our study was simply not strong enough. Against this hypothesis, however, speaks that the increase in threshold compared to baseline in our study was identical to Ferrè et al. (2013). Further studies should clarify the intriguing possibility that real and illusory self-motion alleviates pain.

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Part III

GENERAL DISCUSSION

7

GENERAL DISCUSSION

In the last chapter of this thesis, I will highlight the main findings of the empirical part and embed them within current research. This will be accompanied by a critical reflection of the empirical work and consequential implications and challenges for future research.

7.1 A DISSOCIATION OF EXPLICIT AND IMPLICIT MEASURES

In the first study, we set out to investigate the influence of visuo-vestibular conflicts on body ownership (Macauda et al., 2015), according to Ferrè & Haggard (2016) a key element of somatorepresentation. To measure self identification with another body an explicit (questionnaire) (Botvinick & Cohen, 1998; Lenggenhager et al., 2007) and an implicit (skin temperature) (Moseley et al., 2008; Rohde et al., 2013; Salomon et al., 2013) proxy were used.

Overall, the explicit measure yielded weaker differences than expected. Although the body swap illusion was most strongly experienced in the congruent mannequin condition, the overall illusion score was rather low in comparison to other studies creating multisensory conflicts between sensory modalities, i.e. visuo-tactile (Petkova & Ehrsson, 2008). The questionnaire also revealed that participants had difficulties in detecting visuo-vestibular congruence. In RHIs or FBIs involving the visual and tactile modality, the detection of congruence is usually not measured explicitly, but it is assumed that healthy participants are perfectly able to correctly detect the congruence of visuo-tactile stimuli (Suzuki et al., 2013, for a discussion). The reason for the poor detection ability may be rooted in the tendency to overweigh visual cues in multisensory integration and the inability to weigh visuo-vestibular cues detached from each other due to the vestibular system's multisensory nature (Berger et al., 2010;

Prsa et al., 2012; Angelaki et al., 2009). Questionnaires are the only tool to measure participants subjective experience of the illusion, but their usefulness is questioned in study 1. Different interpretations of the questions, expectations of the illusion and personality factors strongly influence participants' answers (Ehrsson, 2012). Considering the problems of these explicit measures, open questions might thus be the better option to ask for the subjective experience of those illusions as they go beyond the predefined concepts used in the standardized questionnaires. Also, RHIs and FBIs have become an easy and affordable tool to demonstrate multisensory integration to a broad audience in public media and thus it will get even more difficult to recruit naive participants. Such subjective evaluations pose a problem for explicit measures (e.g. expectancy bias), but hopefully not for objective and implicit measures. most strongly In contrast, the temporal pattern of the implicit measure for body ownership, i.e. skin temperature, behaved as predicted. Skin temperature on the hands strongly decreased in the visuo-vestibular congruent mannequin condition. This temperature decrease was not found on the neck. Skin temperature changes as a measure for body ownership were first introduced in a RHI by Moseley and colleagues (2008) and later successfully replicated for the full body (Salomon et al., 2013). Yet, there are substantial differences in the magnitude of temperature changes between those studies. In comparison to Moseley and colleagues' RHI (2008) that showed large temperature decreases, the findings from Salomon et al. (2013) and us (Macauda et al., 2015) suggested rather subtle changes. Physiological mechanisms for the temperature decrease are currently unknown but have to be carefully examined to establish skin temperature as a valid measure for body ownership. In fact, in an attempt to replicate skin temperature changes in a robot induced visuo-tactile RHI, Rohde and colleagues (2013) failed to find temperature decreases specificly for visuo-tactile congruence. It is possible that other unpublished studies measured skin temperature as well but did not find an effect, causing a publication bias and a resulting over-estimation of the true effect size (Etz & Vandekerckhove, 2016). Thus, pre-registered and high-powered replication studies (Wagenmakers et al., 2016, as an example) are necessary to proclaim skin temperature as a valid proxy for body ownership.

To summarize, the skin temperature decrease did not predict the subjective experience of the illusion. While this contrasts with classical findings (Botvinick & Cohen, 1998; Moseley et al., 2008), the dissociation of implicit and explicit proxys is in line with a number of other recent studies on bodily self-consciousness (Abdulkarim & Ehrsson, 2016; Rohde et al., 2013; Rohde, Di Luca, & Ernst, 2011; Elk, Karinen, Specker, Stamkou, & Baas, 2016; Holle, McLatchie, Maurer, & Ward, 2011). For example Abdulkarim & Ehrsson (2016) found that the experimental manipulation of the proprioceptive drift during a RHI did not influence the subjective experience of the illusion. Hence, it is hypothesized that the implicit and the explicit proxy rely on two different processes that influence each other only under certain conditions (Rohde et al., 2011; Abdulkarim & Ehrsson, 2016). A new overarching model for body representation within the framework of predictive coding (Limanowski & Blankenburg, 2013; Hohwy, 2013) might help to establish these conditions. In predictive coding perception is seen as an active process of hypothesis generation and testing with the ultimate goal of prediction error minimization in a Bayesian framework. This process strongly relies on acquired *prior* information. Similarly, Metzinger (2004) proposes that the self is the central product of a generative model of the world - including a representation of the own body and its location - which is necessary for action planning and decision making. Thus, even core aspects of bodily self-consciousness underlie the principle of error minimization. This is seen in bodily illusions caused by multisensory conflicts leading to massive prediction errors. In order to minimize them, body ownership over fake bodies or hands is accepted.

7.1.1 *Implicit measures in disorders of bodily self-consciousness*

The discussion of implicit versus explicit measures is not only limited to multisensory integration paradigms, but is also highly relevant for psychiatric or neurological research, where the characterization of disorders strongly relies on subjective experiences. Thus, in study 2 we set out to study the association between explicit and implicit preferences for body images and to develop objective parameters. The study was based on a failed reduction of the amputation desire in participants with xenomelia through CVS (Lenggenhager et al., 2014). The negative findings showcased the limits of the vestibular influence on an oversimplified model of xenomelia that involves only a disruption of the *minimal* self. In fact, in such a reduced view of xenomelia the *narrative* self and its interaction with the *minimal* self is neglected. Thus, in study 2 we set out to investigate the *narrative* self in individuals with xenomelia. We measured the implicit and explicit association to complete and incomplete bodies in individuals with xenomelia, amputees and normally limbed controls, and found that participants with xenomelia on an explicit level strongly preferred amputated bodies in comparison to amputees and normally limbed controls, who prefered complete bodies. This finding is not surprising as the explicit wish to possess an incomplete body is a core aspect of xenomelia. We also found that participants with xenomelia showed a weak implicit preference for incomplete bodies, especially in comparison to normally limbed controls and amputees, who both showed a strong bias towards complete bodies. The choice to include the latter group enabled us to infer the implicit attitudes in a group where the physical body matches an incomplete body and compare those to individuals where the physical body is complete but the own body image matches the one of amputees. Interestingly, implicit preferences did not predict the explicit outcome. However, the adaption of of our IAT from a racial IAT (Greenwald et al., 1998) bears some risks in the interpretation of its outcome. As the IAT measures the automatic associations between the affective connotations of complete and incomplete bodies and positive or negative attributes, it is difficult to deduce whether those associations are self directed or whether they translate to the evaluatoin of a whole group. An IAT using concepts related to the self or others coupled with complete or incomplete bodies could shed light on how individuals with xenomelia and amputees perceive their own bodily identity implicitly. This type of IAT has been successfully used to determine the implicit gender identity in children with Gender Dysphoria (Olson et al., 2015).

Other implicit measures based on reaction times such as a motor imagery task of limbs (Nico, Daprati, Rigal, Parsons, & Sirigu, 2004), could be adapted for individuals with xenomelia to infer latent parameters underlying their decision making from a hierarchical drift diffusion model (Wiecki, Sofer, & Frank, 2013). Further, those implicit decision parameters could be linked to electrophysiologic processes in electroencephalography (EEG) studies (Schiller et al., 2016, as an example for how to combine EEG and the IAT).

To contribute to the discussion of implicit and explicit measures, xenomelia research has to face important issues, in particular the unknown prevalence (First, 2005). Most studies have been conducted in the United States, Germany, Switzerland and the Netherlands. The focus on this specific countries may be linked to a lack of public awareness of the condition in other countries(Sedda, 2017). To raise awareness, it is important to draw reasonable inferences from the scientific studies the few individuals with xenomelia decide to participate in. Internet experiments are a possible tool to reach this aim. In comparison to laboratory studies, physical presence is not required and individuals with xenomelia can even participate anonymously. Yet, the use of internet experiments is limited to certain research questions and accompanied by other drawbacks discussed in study 2. Another possible solution to ensure reasonable powered studies, consist in multiple laboratories that participate in examining the same research questions (Wagenmakers et al., 2016, as an example). Interested research groups located in different countries or even on different continents could decide a priori on important research questions and the resulting implementations in experimental designs so that data could be pooled. The study coordination of such multicentric studies has been simplified by the recent emergence of online tools such as the Open Science Framework that provides a platform for sharing research protocols and materials.

7.1.2 *Implicit and explicit measures in pain perception*

The advantages and disadvantages of subjective and objective ratings are further discussed in study 3, although not to the same degree as in study 1 and 2. In this third study we investigated the influence of *natural* vestibular stimulation on *somatosensation*, the lowest level of body representation (Ferrè & Haggard, 2016). The use of *natural* vestibular stimulation for pain relief has been proposed for thousands of years (Grabherr et al., 2015), but has only recently been tested systematically with *artificial* vestibular stimulation by the means of CVS. (Ferrè et al., 2013, 2015).

7.1.3 *Pain modulating effects of illusory self-motion?*

We showed that *natural* vestibular stimulation lead to an increase in heat pain thresholds in healthy participants. Importantly, increased heat pain thresholds were also found for visual optokinetic stimulation conditions (Brandt et al., 1973) and for a condition that presented randomly moving dots. The optokinetic sitmulation conditions were included to test whether a possible analgesic effect was related to the specifics of the natural vestibular stimulation or to illusory self-motion in general. However, the increased pain thresholds in the random dots condition suggest an unspecific analgesic effect of distraction rather than pain modulations related to vestibular processing.

If the pain relief was caused by the induced illusory self motion, the vestibularly induced pain relief might not only act on the level of somatosensation but also somatorepresentation. Illusory self motion could lead to a change in self-location and thus alter pain perception through manipulations of bodily self-consciousness. Similarly, it has been shown that that self identification - next to self location another central aspect of somatorepresentation - with an avatar decreased skin conductance responses to painful stimuli (Romano, Pfeiffer, Maravita, & Blanke, 2014). In comparison to Romano and colleagues' (Romano et al., 2014) use of implicit measures for pain processing, we used explicit pain thresholds of the noxious stimuli as well as implicit electrophysiological responses to thermal pain events (Contact Heat Evoked Potentials) similar to Ferrè and colleagues (Ferrè et al., 2015). Unfortunately, the implicit measures contained several missing values and were generally unreliable (see also the Supplementary Material of study 2). As already discussed in section 4 and 5, explicit outcomes depend on high-level processes and are thus prone to cognitive biases. In addition, each threshold was measured only once per condition and participant following a standardized clinical protocol. This one-measure approach probably provoked substantial measurement error, but was the only feasible method given the temporal constraints of the study. As a consequence, future studies should possibly increase the number of trials per condition and include precise implicit, objective and physiological parameters to measure pain responses such as a whole-brain EEG system and skin conductance responses.

7.1.4 *The importance of natural and artificial vestibular stimulation*

The findings from Ferrè and colleagues (2013, 2015) and study 3 (Macrea et al., 2016) are especially relevant to investigate whether the idea to prescribe natural vestibular stimulation as a pain therapy in the form of hanging beds, rocking chairs or a smooth rocking of children (Grabherr et al., 2015) actually relies on vestibular effects. While Ferrè and colleagues' (2013, 2015) results obtained with *artificial* vestibular stimulation would ascribe the analgesic effect to the activation of the vestibular system, the results from study 3 suggest that it could be attributed to rather unspecific shifts of attention away from painful stimuli (Macrea et al., 2016). Such shifts of attention have been identified as a powerful therpeutic tool to modulate the perceived intensity and unpleasantness of pain (Miron, Duncan, & Bushnell, 1989; Melzack & Casey, 1968; Bantick et al., 2002). Hence, the increased pain thresholds in study 3 found in the conditions with natural vestibular stimulation and in the conditions using visual stimuli (optokinetic stimulation and random dots) could be explained by two different analgesic mechanisms (vestibular versus attentional). However, to disentangle the effects of attention from vestibular activity caused by the motion of the chair, elaborated control conditions where the attention load is constant in every condition are necessary. Patients with bilateral vestibular hypofunction or loss constitute an ideal control population as they would undergo the same procedure as healthy participants and experience the same attention shifts caused by the vestibular stimulation but without their vestibular system being stimulated. This would only hold true if the activation of the vestibular system and attention shifts were orthogonal to each other. Interestingly, the interaction of attention and vestibular stimulation is a topic of debate in current vestibular research (Grabherr et al., 2015, for a current summary). While it is hypothesized that attentional networks may overlap with parieto-temporal areas targeted by vestibular stimulation (Oppenländer et al., 2015), attention shifts due to CVS are not always observed in healthy participants (Rorden, Karnath, & Driver, 2001). Importantly, both potential explanation mechanisms act on an implicit level and are not distinguishable by subjective reports.

Independently from how CVS truly affects pain processing, subjective reports and electrophysiological (objective) results provide evidence for its usefulness as a pain reliever. Thus, further studies might give more insight into the underlying neural mechanism. Based on the identified cortical network, real-time fMRI could accordingly be used to develop affordable and explicit pain-relieving cognitive strategies in a therapeutic environment.

7.2 THE RISE OF VIRTUAL REALITY TO STUDY BODILY SELF-CONSCIOUSNESS

While writing this thesis, virtual reality systems with HMDs have emerged and become widely affordable for both, research and leisure. Those systems help to create an unprecedented feeling of immersion within virtual realities. This was especially helpful in study 1, where a new HMD allowed us to present participants another perspective while environmental visual cues from their real position were blocked. Thus, participants' visual attention was completely dedicated to the fake body, which would not have been possible with the presentation of a fake body on a large screen. The attention captive feature of the HMD was also taken advantage of in study 3 as already discussed intensively. The immersiveness could thus play an important role for future pain therapies, combining virtual realities and the embodiment of avatars (Romano et al., 2014). Virtual realities can also be adapted to reach a better understanding of psychiatric disorders and subsequently develop new therapies. Bodily illusions in Virtual Reality have successfully been implemented to improve the body image in anorexia nervosa (Keizer, Elburg, Helms, & Dijkerman, 2016). Similar paradigms could also be applied to individuals with xenomelia in order to depict their perceived own body image as well as to let them simulate the feeling of owning a visibly incomplete body. The amputated body could be experienced both from a first person perspective and the third person perspective. The latter perspective could also give insight to social aspects of xenomelia discussed in study 2.

Nevertheless, such immserive systems are also accompanied by physiological challenges: when wearing those HMDs visuo-vestibular conflicts may arise due to wrongly calibrated systems or head movements provoking vestibular stimulation that does not match the visual input from the HMD. Consequences of a prolonged immersion in such virtual realities are currently unknown. Yet, the recent advance of HMDs demands a filling of this knowledge gap, with a special interest in how visuo-vestibular conflicts interact with the embodiment of virtual avatars and psycho-physiological changes in the real body.

7.3 CONCLUSION

This thesis addressed various aspects of body representation with a special focus on the influence of *natural* vestibular stimulation on somatosensation (study 3) and somatorepresentation (study 1). For the first time, visuo-vestibular congruence was successfully manipulated to induce body ownership over a fake body demonstrating the importance of the vestibular system in bodily self-consciousness (study 1). Moreover, the neurological roots of xenomelia were de-emphasised by showing that the disorder is highly complex and that also implicit mechanisms contribute to this specific disturbance of bodily self-consciousness (study 2). The importance of conceptual replications was highlighted in study 3. We showed that previous findings on the analgesic effect of vestibular stimulation may be not translatable to *natural* vestibular stimulation and might be confounded by shifts of attention. Lastly, this thesis does not have the aspiration to provide definite answers to the raised questions, but to elaborate on previously established gaps of knowledge in the interdisciplinary field of vestibular cognition and bodily self-consciousness.

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Part IV

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Part V

APPENDIX

Supplementary Material to:

Reducing pain by moving? A commentary to Ferrè et al. (2013)

1. Supplementary methods

1.1 Participants

20 healthy, right-handed (according to the Edinburgh handedness inventory (Oldfield, 1971)) men participated. Only participants with normal Quantitative Sensory Testing (QST) parameters (Maier et al., 2010) at the baseline measurement were included in the sample. All participants gave written informed consent. The study protocol was approved by the local ethic committee and was in accordance with the principles of the Declaration of Helsinki 2008 and the guidelines of Good Clinical Practice (clinicaltrials.gov Identifier: NCT02358954).

1.2 General procedure

Participants underwent two experimental blocks (see Figure S1), which were presented in counterbalanced order.

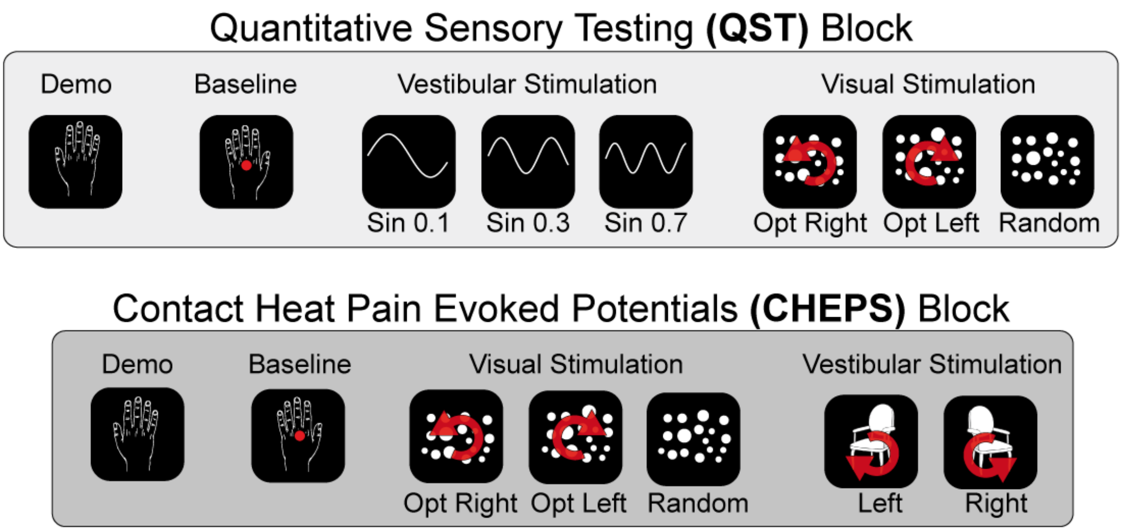

Figure S1: Complete experimental procedure. The two experimental blocks (QST block and CHEPS block) were presented in counterbalanced order. For each block, a demonstration (demo) was first performed on the right hand in order to familiarize the participant with the method, always followed by a baseline measurement on the left hand, followed the two experimental mini-blocks (visual and vestibular) which were presented in counterbalanced order. The conditions within the mini-blocks were counterbalanced as well. The red arrow corresponds to the (illusory) movement of the participants.

1.2.1. Quantitative Sensory Testing

In the *QST block* quantitative sensory testing was used on the dorsum of the left hand to assess the following subjective thresholds: Cold detection threshold (CDT), Warmth detection threshold (WDT), Cold pain threshold (CPT) and Heat pain thresholds (HPT). QST parameters were acquired according to the standardized protocol of the German Research Network on Neuropathic Pain (Maier et al., 2010; Rolke et al., 2006) using the methods of limits (temperature slope, 1°C/s; baseline temperature 32°C) with the TSA 2001-II device (MEDOC, Ramat Yishai, Israel).

1.2.2 Contact Heat Evoked Potentials

In the *CHEPS block* we assessed contact heat evoked potentials induced by a heat pulse stimulator (CHEPS, Medoc Ltd., Ramat Yishai, Israel) attached to the dorsum of the left hand. The thermode, with a contact activation area of 573 mm^2, uses a combination of a heating foil and a Peltier element to generate the fast heating and cooling rate. We used the maximum rates available (a heating rate of 70 °C/s and a return rate of 40 °C/s). The stimulus duration was approximately 800ms (271ms from baseline to peak temperature and 475ms to return to baseline (Roberts et al., 2008)). CHEPs were sampled at 2 kHz using a single channel preamplifier (bandpass filter 0.25-300 Hz, ALEA Solutions, Zurich, Switzerland). The heat pulses were applied from a baseline temperature of 32 °C to a peak temperature of 52°C with an inter-stimulus interval that varied randomly between 8 and 12 s (end-to-onset interval) on the dorsum of the left hand (Kramer, Haefeli, & Jutzeler, 2012).

1.3 Vestibular stimulation

Subjects were seated upright on a 3D-turntable with three servo-controlled motor-driven axes (conceived by Prof. V. Henn, designed and manufactured prototype built by Acutronic, Switzerland). Only rotations around the earth vertical (yaw) axis were used in the current experiment. The head was restrained with an individually moulded thermoplastic mask (Sinmed BV, Reeuwijk, Netherlands). Subjects were positioned so that the intersection of the inter-aural and naso-occipital axes was at the intersection of the three axes of the turntable. Pillows and safety belts minimized movements of the body.

1.3.1 Vestibular stimulation during QST

In order to assess the effects of vestibular stimuli on pain thresholds, a sustained constant natural vestibular activation over the time of the QST was necessary. As perceptual responses to sustained angular motion stimuli decay over time (Bertolini et al., 2011; Okada, Grunfeld, Shallo-Hoffmann, & Bronstein, 1999), we decided to use an oscillatory motion profile of the chair with three frequencies: 0.1, 0.3 and 0.7 Hz, defined as Sin 0.1, Sin 0.3 and Sin 0.7. The peak velocity (the relevant stimulus for the vestibular system) was 30 deg/s at all frequencies. Testing of sinusoidal stimuli at different frequencies was necessary to obtain a sustained cover of the spectrum of natural angular stimulation of the vestibular response (Fernandez & Goldberg, 1971; Leigh & Zee, 2006) and, concurrently, provided a frequency response characterization in line with previous vestibular studies (Bockisch, Straumann, & Haslwanter, 2005).

1.3.2 Vestibular stimulation during CHEPS

As evoked potential in CHEPS occurs over a time span < 1 s, we used a natural vestibular stimulus consisting of a 120 deg impulsive rotation with a maximal rotation of 450 deg/s. The chair movement was synchronized with the evoked potentials and the thermic stimulus arrived 300 ms after initiating the movement. The difference between the stimuli used for the threshold measurements (sinusoidal stimuli) and those for evoked potential measurement (impulsive stimuli) allowed matching the time scale of the vestibular stimulation to that of each measurement. We defined chair left as the passive counter clockwise and chair right as the passive clockwise rotation.

1.4 Visual Stimulation

Full-field visual stimulation consisting of white dots of different sizes moving on a black background at 30 deg/s was used. A head mounted display (Oculus Rift, Oculus, Irvine, USA) provided the visual stimuli created in ExpyVR (http://lnco.epfl.ch/expyvr). In the "optokinetic stimulation left" and the "optokinetic stimulation right" conditions the dots were coherently moving to the right or left respectively, inducing illusory self-motion (vection; Brandt et al., 1973) to the left or right, respectively. In the "random dots condition" the dots were moving incoherently in random directions, inducing therefore an overall null visual motion and no self-motion illusion.

1.5 Measurements

1.5.1 Subjective thresholds in the QST block

Participants had to press a button as soon as they felt the slightest change of temperature to “cold” or “warm” (cold detection threshold (CDT) or warmth detection threshold (WDT), respectively). For the cold pain threshold (CPT) and heat pain threshold (HPT) participants had to press the stop button immediately at the first painful sensation. Each measure was repeated 3 times for each condition and a mean threshold temperature was calculated. All thresholds were obtained with ramped stimuli (1 °C/s) that were terminated when the subject pressed a button. For thermal detection thresholds the ramp back to baseline was 1 °C/s, while for thermal pain thresholds this ramp was chosen at maximum device capacity resulting in nominal ~5 °C/s (Rolke et al., 2006).

1.5.2 Pain intensity ratings during the CHEPS block

The perceived pain intensity was assessed after each of the 10 stimulations per condition according to a 0 to 10 numerical rating scale (NRS). An auditory cue 2 seconds after stimulation indicated the participants to verbally tell the experimenter the intensity rating (Kramer et al., 2012).

1.5.3 Cortical pain evoked potentials during the CHEPS block

Cortical recording electrodes were positioned according to the International 10-20 system based on available guidelines (Cruccu et al., 2008). N2/P2 was acquired from an active vertex-recording electrode (Cz) referenced to the nose. A contralateral temporal active recording electrode (T4) referenced to Fz was used to acquire N1/P1 potentials.

1.5.4 Motion sickness during both blocks

The sensitivity to motion sickness differs strongly between individuals (Golding & Gresty, 2015; Lackner, 2014). To quantify the possible influence of motion sickness on our results, we monitored its level after each stimulation trial using a simplified Pensacola scale from 0 to 20 (Dai, Kunin, Raphan, & Cohen, 2003).

1.5.4 Self-motion during all visual stimulations

A Visual Analog Scale (VAS) scale (0= no self-motion, 10 = strong self-motion) after the two optokinetic stimulations and the presentation of the random dots was used in order to assess intensity of induced illusory self motion.

1.6 Statistical Analysis

Statistical analysis was performed using the statistical programming language R version 3.0.2 (http://www.**r-project**.org/) including the BayesFactor package (Rouder, Morey, Speckman, & Province, 2012) and WRS2 package (WRS2: Wilcox robust estimation and testing; Mair, Schoenbrodt, & Wilcox, 2015).

1.6.1 QST data

The raw QST data was transformed to temperature changes by subtracting the baseline values from each condition. We first run Bonferroni-corrected ($p = .008$) one-sample t-test for each difference to test whether they were significantly different from zero, i.e. baseline. We then used a one-way ANOVA for all conditions Sin 0.1, Sin 0.3, Sin 0.7, Optokinetic Stimulation Right, Optokinetic Stimulation Left, Random dots).

1.6.2 CHEPS data

Pain intensity rating

As baseline N1 potentials were missing, we excluded six participants from all CHEPS data analyses (new $n = 14$). The raw NRS data was transformed to pain perception changes by subtracting the baseline values from each condition. We first ran Bonferroni corrected ($p = .01$) one sample t-test for each difference to test whether they were significantly different from zero, i.e. baseline. Afterwards a repeated measures one way ANOVA was calculated with the following conditions: Vestibular Stimulation left, Vestibular Stimulation right, Optokinetic Stimulation Right, Optokinetic Stimulation Left, Random dots.

Pain evoked potential data

Potentials were manually detected and where considered not present if we could not detect a peak wave in relation to the background small unreliable CHEPs (<10µV) were discarded (Haefeli, Kramer, Blum, & Curt, 2013). In case no potential was detected the amplitude was coded as 0 (see Untergehrer, Jordan, Eyl, & Schneider, 2013 for a comparable approach). We first ran Bonferroni corrected (p=0.01) one sample t-test for each difference to test whether they were significantly different from zero, i.e. baseline. Afterwards a repeated measures one way ANOVA was calculated with conditions (Vestibular Stimulation left, Vestibular Stimulation right, Optokinetic Stimulation Right, Optokinetic Stimulation Left, Random dots) for the amplitudes of N1, N2 and P2.

2. Supplementary results

The descriptive results are shown in Table S1 and S2.

	Baseline	Sin01	Sin03	Sin07	Vest. stim left	Vest. stim right	Opt. kin. left	Opt. kin. right	Random Dots
HPT	45.29 (± 2.60)	46.86 (± 3.49)	47.24 (± 2.81)	47.28 (±2.93)			47.44 (± 2.17)	47.49 (± 2.45)	47.13 (± 2.33)
CPT	16.56 (± 9.73)	15.54 (± 9.74)	14.27 (± 9.42)	13.97 (± 10.06)			14.49 (± 10.00)	14.77 (± 10.76)	14.31 (± 10.15)
WDT	34.09 (± 0.87)	38.18 (± 2.87)	38.39 (± 2.79)	38.53 (± 2.50)			39.20 (± 2.60)	39.23 (± 3.06)	38.68 (± 2.82)
CDT	30.69 (± 0.67)	29.02 (± 2.43)	28.23 (± 3.99)	29.84 (± 3.56)			28.67 (± 2.81)	28.46 (± 2.64)	28.82 (± 2.23)
NRS-Pain	1.94 (± 1.00)				1.71 (± 1.07)	1.51 (± 1.05)	1.19 (± 0.78)	1.49 (± 0.85)	1.84 (± 1.25)
N1 A	-8.02 (± 3.50)				-11.73 (± 9.26)	-6.40 (± 6.01)	-3.63 (± 3.18)	-4.06 (± 3.55)	-5.61 (± 4.80)
N2 A	-9.40 (± 3.97)				-8.04 (± 5.34)	-8.48 (± 6.14)	-5.09 (± 4.04)	-5.58 (± 3.87)	-5.97 (± 4.68)
P2A	9.41 (± 4.46)				8.15 (± 5.10)	6.62 (± 4.18)	3.72 (± 2.83)	5.72 (± 4.33)	5.22 (± 4.99)

Table S1. Means (± standard deviations). HPT, CPT, WDT and CDT are shown in °C.

	Sin01	Sin03	Sin07	Opt. kin. Left QST	Opt. kin. Right QST	Random Dots QST	Vest. stim left	Vest. stim right	Opt. kin. Left CHEPS	Opt. kin. Right CHEPS	Random Dots CHEPS
Motion-Sensation				4 (+- 2.71)	4.45 (+- 2.63)	1.5 (+- 1.67)			4 (+- 3.04)	4.29 (+- 2.97)	0.71 (+- 1.44)
Pensacola	0.65 (+- 1.14)	0.60 (+- 0.99)	0.65 (+-1.14)	1.10 (+- 1.45)	2.05 (+- 2.80)	0.65 (+- 2.06)	0.35 (+- 0.74)	0.92 (+- 1.44)	1.21 (+- 2.26)	1.36 (+- 2.21)	0.14 (+- 0.53)

Table S2. Means (± standard deviations)

2.1 QST

2.1.1 Cold pain thresholds

The one sampled t tests revealed that there were no differences significantly different from zero (all $p > .11$). The repeated measures ANOVA showed no effect of condition ($F(3.10, 58.94) = 1.54$, $p = .21$).

2.1.2 Warmth detection thresholds

The one sampled t tests revealed that all differences were significantly different from zero (all $p < .001$). The one-way ANOVA showed no effect of condition ($F(5,95) = 1.14$, $p = .0.35$).

2.1.3 Cold detection thresholds

Wilcoxon signed rank tests revealed that all differences were significantly different from zero (all $p < .003$).

2.2 NRS data

One sample t-tests revealed a difference significantly different from zero for the condition Optokinetic Stimulation right ($p < 0.001$). All other conditions t-tests showed no significant difference from zero (all $p > .022$). For the ANOVA, Mauchly's test indicated that the assumption of sphericity had been violated, therefore degrees of freedom were corrected using Huynh–Feldt estimates of sphericity ($e = .74$). The results show that the difference in pain perception was not significantly affected by the condition, $F(2.92, 38.48) =.1.68$, $p = 0.18$. The Bayesian ANOVA revealed a Bayes Factor of 0.44, i.e. slightly more evidence for the null hypothesis, yet more data would be needed for conclusive results.

2.3 Pain evoked potential data

2.3.1 N1 Amplitude

T-tests revealed a significant difference (i.e. a smaller amplitude) from zero for the condition Optokinetic Stimulation right and Optokinetic Stimulation left (all p-values < 0.01). All other conditions t-tests showed no significant difference from zero (all $p > .04$). For the ANOVA Mauchly's test indicated that the assumption of sphericity had been violated, $p < .001$, therefore degrees of freedom were corrected using Huynh–Feldt estimates of sphericity ($e = .37$). The results show that the difference in the N1 amplitude was significantly affected by the condition, $F(1.48, 19.24) = 8.17$, $p = .005$.

2.3.2 N2 Amplitude

T-tests revealed a significant difference (i.e. a smaller amplitude) from zero for the condition Optokinetic Stimulation left ($p < .01$). All other conditions t-tests showed no significant difference from zero (all $p > .03$). For the ANOVA Mauchly's test indicated that the assumption of sphericity had been violated, $p < .001$, therefore degrees of freedom were corrected using Huynh–Feldt estimates of sphericity (e = .56). The results show that the difference in the N2 Amplitude was not significantly affected by the condition, $F(2.24, 29.12) = 1.92$, $p = .16$.

2.3.3 P2 Amplitude

T-tests revealed a significant difference (i.e. a smaller amplitude) from zero for the condition Optokinetic Stimulation left and right ($p <.01$). In all other conditions t-tests showed no significant difference from zero (all $p > .01$). For the ANOVA Mauchly's test indicated that the assumption of sphericity had been violated, $p < .001$, therefore degrees of freedom were corrected using Huynh–Feldt estimates of sphericity (e = .56). The results show that the difference in the P2 amptliude was significantly affected by the condition, $F(2.32, 30.16) = 1.92$, $p = .03$.

2.4 Additional analyses

2.4.1 Motion sickness

For the motion sickness data a Friedman test revealed a significant effect of condition in the QST block ($X^2(5)=12.43$, $p = 0.03$) and in the CHEPS block ($X^2(4)=10.74$, $p = 0.03$).

2.4.2 Motion rating during visual stimulation

Optokinetic stimulation of coherently moving white dots to the left and right did induce a slight egomotion sensation (vection) during the QST ($X^2(2)=19.97$, $p < .001$) and the CHEPS block ($X^2(2)=20.91$, $p < .001$). Wilcoxon tests were used to follow up this finding. A Bonferroni correction was applied and so all effects are reported at a .016 level of significance. This analyses revealed higher motion sensations during both Optokinetic Stimulation right (W=316.5, p=0.001) and Optokinetic Stimulation left (W=332, p<0.001) in the QST as well in the CHEPS block (Optokinetic Stimulation right: W=171, p<0.001 and Optokinetic Stimulation left: W=167, p=0.001) as compared to the Random dots condition. The two Optokinetic

Stimulation conditions did not differ significantly neither in the QST (W=177.5, p=0.54) nor in the CHEPS block (W=91, p=0.76)

3. Supplementary discussion

Next to the main finding, reported in the manuscript our supplementary results suggest the following additional findings.

First, while the heat pain threshold was increased compared to baseline in all conditions (see main text), the cold pain threshold was not altered by any of our experimental manipulations. This findings could potentially be linked to differential physiological mechanisms underlying cold and warmth perception (e.g. Schepers & Ringkamp, 2010), or, alternatively, to the very large population standard deviation (mean 13.69°C; standard deviation 9.54) of the cold pain threshold (Maier et al., 2010), which might make the identification of a variation between conditions more difficult. *Second*, our data show that vestibular and optokinetic stimulation, as well as incoherently moving random dots influence thermal detection thresholds (warmth and cold detection) similar to pain detection thresholds, by generally decreasing sensitivity, i.e. warmth detection threshold was increased and cold detection threshold decreased during all stimulations as compared to baseline. *Third*, we could not show a decrease in the subjective evaluation of the pain during our CHEPs measurements Ferré and co-authors (2013) did in three subjects (experiment 2 of their study). This might be related to methodological differences, but could also question a general pain reduction induced by the vestibular stimulation (see also discussion in the main text). *Forth*, the electrophysiological data on the pain evoked potentials showed generally and contradictory to (Ferrè, Haggard, Bottini, & Iannetti, 2015), no influence of the vestibular stimulation on neither N1, N2 or P2. Amplitudes of N1 and P2 were both significantly reduced compared to baseline in both the optokinetic stimulation left and right condition, while N2 was reduced specifically in the optokinetic stimulation left condition. These data were however not corroborated by the subjective measure as by the pain ratings (see above), which did not differ from zero in any of the conditions. The electrophysiological results have to be considered with caution, as only 14 participants could be included due to missing clear typical pain-evoked components in the others. Moreover, with the current setup it is not possible to exclude that the effect could be linked to eye-movements. Both vestibular and visual motion stimuli induce reflexive eye movements, which, even if we carefully checked that participants always fixated a red dot, evoke neural activity required to suppress the reflex. The current setup did not allow correcting for eye movements or eye movement suppression, which might have been strongest in the two optokinetic stimulation conditions. Alternatively, and more interestingly, the effect could be linked to motion sickness. Motion sickness is known to affect performances and reaction time already in case of sopite syndrome, i.e. conditions occurring at the onset of motion sickness or in presence of very mild nauseogenic stimuli, in which the symptoms are so low that the participants are often not able to recognize or report them (Lackner, 2014). In our experiment motion sickness was overall very low, but the highest values were found in both left and right optokinetic stimulation conditions, and is plausibly high as well during caloric vestibular stimulation (Ferrè et al., 2013; Ferrè et al., 2015), and could thus have mediated implicit nociceptive processes.

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The moving history of vestibular stimulation as a therapeutic intervention

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Abstract

Although the discovery and understanding of the function of the vestibular system date back only to the 19th century, strategies that involve vestibular stimulation were used long before to calm, soothe and even cure people. While such stimulation was classically achieved with various motion devices, like Cox's chair or Hallaran's swing, the development of caloric and galvanic vestibular stimulation has opened up new possibilities in the 20th century. With the increasing knowledge and recognition of vestibular contributions to various perceptual, motor, cognitive, and emotional processes, vestibular stimulation has been suggested as a powerful and non-invasive treatment for a range of psychiatric, neurological and neurodevelopmental conditions. Yet, the therapeutic interventions were, and still are, often not hypothesis-driven as broader theories remain scarce and underlying neurophysiological mechanisms are often vague. We aim to critically review the literature on vestibular stimulation as a form of therapy in various selected disorders and present its successes, expectations, and drawbacks from a historical perspective.

Keywords: historical perspective, vestibular system, motion device, caloric vestibular stimulation, galvanic vestibular stimulation, treatment

"Nothing happens until something moves." (Albert Einstein)

Artistotle's famous description of the five senses (i.e. sight, audition, smell, touch and taste) has not only informed lay understanding but also "guided the [scientific] study of perception for two thousand years" (Wade, 2003, p. 151). Although phylogenetically very old (e.g. Goldberg and Fernández, 2011), the vestibular system and its functions were discovered and described only in the 19th century, most prominently by Flourens (1830), Purkinje (1820) and Ménière (1861). Marie Jean Pierre Flourens (1830), for example, observed that pigeons showed oscillatory eye movements and postural impairments after a labyrinthectomy. This finding was surprising and informative, because at that time the anatomy of the labyrinth was known, but its function was attributed to auditory perception. Thus, the labyrinth seemed clearly to be implicated in other ways than previously thought of.

Today, the vestibular system, which includes sensors detecting three-dimensional linear (otoliths) and angular (semicircular canals) acceleration, is - at least in the scientific community - accepted as a "sixth sense". Its important roles in the control of posture, balance and eye movements have been intensively studied. Besides these more basic functions, the investigation of vestibular contributions extends to various fields of clinical and cognitive neuroscience (for reviews, see e.g. Gurvich et al., 2013; Lenggenhager and Lopez, in press; Mast et al., 2014; Palla and Lenggenhager, 2014; Pfeiffer et al., 2014; Smith and Zheng, 2013). Especially the study of the cognitive aspects of vestibular stimulation, though already highlighted by Griffith (1922) has recently gained importance. Despite this new trend, insights and knowledge, especially concerning its cortical representations, are still rather limited compared to other senses (for a brief discussion see e.g. Mast et al., 2014).

Contrasting the late discovery and limited understanding of the neurophysiological mechanisms, vestibular stimulation has often been suggested as a cure for various clinical disorders, and provided some seemingly surprising data suggesting for example increased eye contact in autistic children (Slavik et al., 1984) and the report of an instant and complete cure of hysterical deafness (McKenzie, 1912). In the following, we will describe how vestibular stimulation has been developed and - with varying success - used in therapeutic contexts over more than 2000 years. The advantages of vestibular stimulation as a therapy and its resulting popularity are evident, given that it is usually non-invasive (even if some of the methods used in the early 19th century would nowadays be regarded as torture), rather cheap and easily applicable. Yet, it is often ignored that vestibular stimulation is highly complex because a) its effects depend on the exact application parameters and b) vestibular stimulation is never pure, requiring elaborate and well-controlled studies.

The aim of this review is to outline and critically discuss the use of therapeutic vestibular stimulation in humans in a historical framework. We will first describe the discovery and development of the three main methods of passive vestibular stimulation, i.e. motion devices, caloric vestibular stimulation (CVS) and galvanic vestibular stimulation (GVS). Then, we will review the literature that investigates the effects of vestibular stimulation on various clinical conditions, including sleep difficulties, mood disorders, chronic pain, bodily disorders, schizophrenia, neurodevelopmental and neurodegenerative disorders. Finally, we will provide a short outlook on the potential of vestibular stimulation for cognitive enhancement. It is important to point out that it is by no means possible to cover all the relevant literature from the field within the scope of this review. It thus represents a selection of those topics and studies that seem most relevant and interesting to us.

1. The discovery and development of vestibular stimulation techniques for humans

1.1. Motion devices

Although cradles, which apply a basic form of passive vestibular stimulation, have existed for a very long time (Jütte, 2009), the first documented therapeutic motion device was probably the so-called 'lectos pensiles' (hanging beds), built by ancient Greek physician Asclepiades of Bithynia (Vieth, 1795). Based on his observations, Roman physician Aulus Cornelius Celsus prescribed the 'lectis suspensi motus' (floating beds) for setting the body in motion to cure 'phrenesis', i.e. 'madness' (for a more exhaustive historical overview, see Jütte, 2009).

The documentation of motion devices reappeared in the 18th century. Despite the fact that Erasmus Darwin (1801) is typically credited for reintroducing a sketch of a motion device (rotating couch) in his work 'Zoonomia' (e.g. Wade, 2005; Wade et al., 2005), it has been argued that it was in fact Christian Gottlieb Kratzenstein and his student Henrico Hövinghoff[1] who had described and built the 'centrifuga', a therapeutic motion device, in the mid-18th century (Jütte, 2009). While Kratzenstein's work has rarely been cited, the English physician Joseph Mason Cox became famous with the so-called Cox chair[2] that he built according to Darwin's idea (Wade, 2005; Wade et al., 2005). He used conventional swings, rotating chairs and rotating beds in the

[1]His medical dissertation "Novum medicinae genus nimirum vim centrifugam ad morbos sanandos adplicatam more geometrarum proponit" from 1765 can be found online (http://www.ub.uni-kiel.de/digiport/bis1800/Kd3153.html).
[2]Pictures from Darwin's drawings of his rotating couch and a photograph of the Cox chair can be found in Wade et al., 2005.

treatment of patients with various pathologies of the asylum where he practiced. A short time later, the Irish physician William Saunders Hallaran developed a chair and a bed (see Fig. 1A) that could be rotated up to 100 times per minute (Breathnach, 2010).

The use of rotating chairs also fueled scientific theories about the vestibular system (Barany, 1907). Around 1820, the Czech physiologist Johannes Evangelista Purkinje (1820) observed systematic eye movement in psychiatric patients during and after their treatment on a rotating chair. He is therefore often identified as the ‘discoverer’ of the nystagmus (Barany, 1907; Breathnach, 2010), although post-rotatory eye movements had already been described by Darwin and Wells (Wade, 2000; Wade et al., 2001). A more detailed description of the vestibular system, including the semicircular canals, was later provided by Ernst Mach and Alexander Crum Brown (Wade, 2000). To test the semicircular canals in more detail, Mach (1875) built a chair within a wooden rotatable frame, allowing horizontal and vertical rotations to investigate the effects of rotations as well as visual orientation in tilted positions (Wade, 2005) (see Fig. 1B). Crum Brown (1874), who was more interested in vestibular thresholds for detecting body rotation, developed a revolving stool, which was less elaborate than Mach’s device (Wade, 2005, p. 200). With Robert Bárány (1907, see Fig. 1C), the interest shifted towards the role of eye movements in vestibular disorders and the rotary chair started being used as a diagnostic tool, which it still is today (e.g. Valente, 2007).

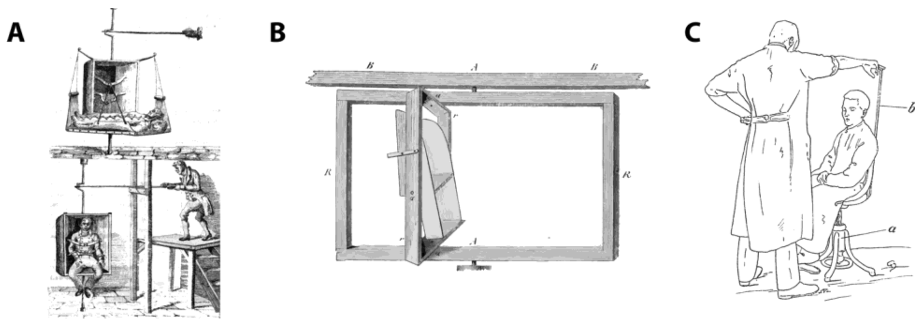

Figure 1. A) a picture of Hallaran’s bed and chair used for therapeutic purposes in an asylum in the beginning of the 19th century (Breathnach, 2010), B) the device used by Ernst Mach for experimental purposes (Mach, 1875) and C) Bárány’s rotating chair that he used for clinical diagnostics (Barany, 1907).

From the 1920s, Dodge’s experiments to investigate rotation thresholds and habituation to rotation stand out (Dodge, 1923a, 1923b). To perform such experiments he needed very slow accelerating motion devices. With the beginning of aeronautic and manned space programs a few decades later, large-scale centrifuges were built to simulate an increase of gravitational force and to study its influence on human physiology and cognition (e.g. Graybiel and Brown, 1951; Kunkle et al., 1948). But other motion devices, such as a slow rotating room, were also developed for the space program (Graybiel et al., 1960). An extensive list of available motion devices is presented in Guedry and Graybiel (1961). Walsh (1961) used another notable device, which stimulated participants while they were immersed in water in a movable tank. This was done in an effort to reduce the co-involvement of the proprioceptive and somatic system as this is one of the important confounds and thus disadvantage of vestibular stimulation through motion devices.

Another milestone in the development of modern motion devices was Stewart's idea of a motion platform with six degrees of freedom, allowing the application of rotations and translations (Stewart, 1965). In contrast to early devices that usually allowed movements around one axis only, on this platform participants can be moved in different directions to stimulate the otoliths and semicircular canals separately or in combination. Nowadays, motion devices are increasingly used for vestibular research (for a review of different ways of stimulating the vestibular system see Palla and Lenggenhager, 2014). The advantage of such devices is that they provide access to precise information about and manipulation of acceleration, acceleration profile and duration of the applied movements.

1.2. Caloric vestibular stimulation (CVS)

Robert Bárány is also credited for introducing CVS as a diagnostic clinical tool. He discovered that irrigating the external ear canals with warm or cold water elicits eye movements in a predictable fashion ((Barany, 1907), see Fig. 2A for a picture of his bedside setup). In fact, exactly 100 years ago, Bárány (1914) was awarded the Nobel Prize of Medicine for his remarkable contributions (Breathnach, 2010; Lopez and Blanke, 2014; Wade, 2005). Thanks to otologists, who routinely prescribed syringing to remove cerumen, it was already known that syringing with warm or cold water could induce vertigo (Goltz, 1870) and provoke eye movements, while use of body temperature water and syringing in an upright position does not lead to these symptoms. Bárány described how one day he irrigated the ear of a patient with cold water. As the patient complained about getting "giddy", he used warmer (accidentally too hot) water and noticed that, curiously, the nystagmus changed direction (Baloh, 2002). This led him to propose the theory of endolymphatic flow, which is still largely accepted today. It is disputed however, how much his colleagues in Vienna contributed to these developments (see Baloh, 2002 for a detailed account on the controversy sourrounding Bárány and the discovery of the caloric test). Importantly, Bárány recognized the value of CVS as a diagnostic tool for peripheral vestibular dysfunctions as it is still used in clinical settings. Bárány himself did not seem to have attributed a therapeutic value to CVS, but such stimulation was later also used in therapeutic settings. Less known is the fact that Bárány

(1907) also described the application of galvanic vestibular stimulation (GVS), the history of which we will outline below.

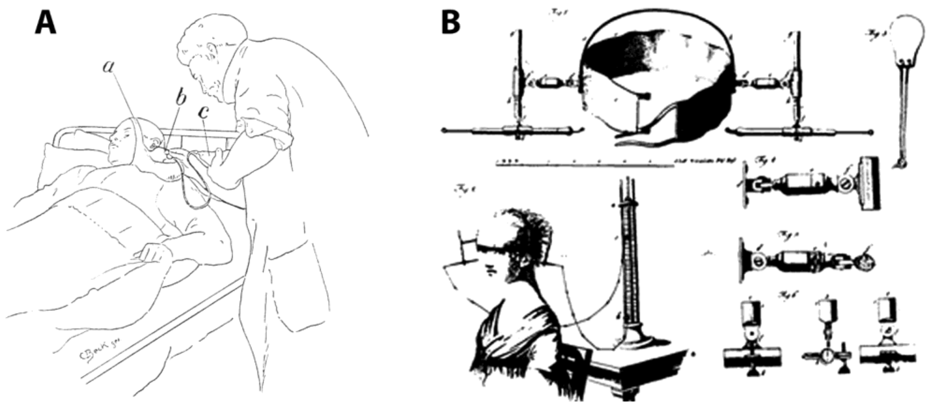

Figure 2. A) Bárány's (1907) bedside caloric test showing *a* rubber bag to collect the water, *b* nozzle for water irrigation, and *c* balloon filled with water (see also Baloh, 2002). B) Early galvanic stimulation device; here used in order to cure tinnitus (Grapengiesser, 1801).

1.3. Discovery and development of galvanic vestibular stimulation (GVS)

The history of GVS (nicely reviewed in Fitzpatrick and Day, 2004) dates back to the beginning of the 19th century. In the context of Alessandro Volta's discoveries, experiments with application of currents behind the ears have been described to evoke sensations of vertigo (Augustin, 1803), even if the underlying physiological mechanisms were still not know. This finding, as well as the fact that such stimulation induces disturbances of equilibrium, nystagmus, and the specific sensation of an illusory tilt towards the cathode, has later on been described by various authors (e.g. Hitzig, 1874) and was finally identified by Josef Breuer (1874) as a phenomenon of vestibular origin. GVS has been suggested early on as a therapeutic method, although initially as a treatment for deafness and tinnitus (see e.g. Rubinstein and Tyler, 2004, for a discussion of the sudden rise and fall of GVS as a cure for auditory deficits, see Fig. 2B for a picture of the setup). While the devices of the first half of the 19th century all used direct current stimulation (thus galvanization), other stimulation methods, for example, using alternating current, soon evolved (Rubinstein and Tyler, 2004).

Nowadays, it is well-known that GVS, transmitted via two electrodes placed over the mastoid process, stimulates and/or inhibits all peripheral vestibular afferents of both the semicircular canals and the otoliths (Goldberg et al., 1984), and the type of stimulation depends on the current's flow (e.g. Fitzpatrick and Day, 2004). The device itself has changed only marginally since its early application, and various relatively cheap, safe and simple stimulators are available, usually consisting of two electrodes and an electrical stimulation device that delivers currents between 0-

3 mA. GVS is now increasingly used in cognitive and neuroscientific research to manipulate vestibular signaling in controlled ways, as - similar to motion devices but unlike CVS - it allows precise timing and coordination with other stimuli (see e.g. Palla and Lenggenhager, 2014, for a review). Below we will review how GVS has been used as a therapeutic tool for various neurological and psychiatric disorders.

1.4.Future directions

While becoming more high-tech and elaborate, the stimulation techniques have, in principle, not changed radically over the last decades (see e.g. Palla and Lenggenhager, 2014, for an illustration of new applications). Nevertheless, for each method, certain trends might be foreseen.

Motion devices can - due to technical advances - be controlled much more precisely in terms of type of motion, intensity, acceleration profile, and duration. New research trends point in two directions. On the one hand, laboratories have started to use top-notch motion devices like the MPI CyberMotion Simulator, which allows continuous motion in different axes and for which a big hall had to be constructed (e.g. Barnett-Cowan et al., 2012). Such large motions devices present great opportunities in basic research, but are less convenient for therapeutic purposes. On the other hand, there are trends to develop relatively small, affordable and easy to use therapeutic home devices (see e.g. Dyk et al., 2008, for a model specifically designed for children), which are more relevant for therapeutic purposes.

New methods for *caloric vestibular stimulation* strive to make its application safer. For instance, air caloric devices are gaining importance (for a discussion of air vs. water CVS, see e.g. Barros and Caovilla, 2012). In the same vein, other techniques such as CVS with near infrared radiation (Walther et al., 2011) or wet air (Gudziol et al., 2012) are being investigated. CVS activates the horizontal canal(s) because of the proximity to the external ear canal. It is still debated whether the vertical canals can also be stimulated by CVS (e.g. Ichijo, 2012, 2011; Shen et al., 2013), but if so, it would broaden the possibilities for applications. Particularly, this could a) allow testing the integrity of the vertical canals and thus be interesting for diagnostic purposes and b) allow to assess the implication of the vertical canals, for example, in an emotion or cognition paradigm and thus be interesting for basic research. Furthermore, increased safety could allow the use of home devices for prolonged and repetitive stimulation, which has shown to be important in some therapeutic setups (see below).

A similar trend towards easier and safer application can be seen for *galvanic vestibular stimulation*. This technique also appeals to developers of virtual reality applications, who see in it a method to increase the feeling of presence in virtual reality (Maeda et al., 2005). This might also be important for the emerging field of VR-based therapeutic interventions and rehabilitation. In this context, GVS as a 'remote-control' has already been used to steer human walking (Fitzpatrick et al., 2006). Apart from such integrative methods, the main progress of GVS over the past might lie in the shift of application and stimulation parameters towards stochastic and sub-threshold galvanic stimulation (see e.g. Oppenländer et al., 2014 for the treatment of visual neglect). Such stimulation does not induce the side-effects typically associated with GVS, like pain on the skin (Lenggenhager et al., 2008), therefore allowing prolonged stimulation duration (e.g. Yamamoto et al., 2005) and allowing vestibular and sham stimulation to switch without the participants' awareness.

2. The use of vestibular stimulation as a therapeutic intervention

The use of vestibular stimulation as a therapeutic instrument dates back to a time long before the physiology and function of the vestibular system were known. Yet, the interest in vestibular stimulation and its potential use in various therapeutic settings strongly increased in the 19th and 20th centuries. In the following chapters, we discuss a selection of interesting observations and studies in which vestibular stimulation has been used as a therapeutic method. We thereby try to judge its success and failure from today's perspective and knowledge.

2.1. Vestibular stimulation for general soothing effects and improving sleep quality

The use of cradles to induce sleepiness in children has already been described in ancient times (Jütte, 2009). Such knowledge of the hypnagogic effect of passive rocking seems culturally universal. There are, for example, reports about its early usage in the Himalaya (Burrows, 1828). However, empirical data on the topic are inconclusive. Some studies found prolonged quiet sleep during vestibular stimulation (Barnard and Bee, 1983; Johnston et al., 1997; Korner et al., 1990), while other studies found that it promoted wakefulness (Campos, 1994; Gregg et al., 1976), which is also in line with literature suggesting an influence of vestibular cues on arousal and sleep regulation (e.g. Horowitz et al., 2005). The velocity of rocking has been suggested to be crucial (Johnston et al., 1997): slower speed is thought to promote sleep (Gregg et al., 1976) while faster speed or a fall is thought to promote wake states (Campos, 1994) or even wake an organism from sleep (Horner et al., 1997). On a neurophysiological level, an animal model showed that the medial vestibular nucleus projects onto hypocretin neurons and thus regulates sleep and arousal (Horowitz et al., 2005).

The first documented use of moving or rocking as a formal treatment probably dates back to the ancient Greek physician Asclepiades of Bithynia (Vieth, 1795). He invented hanging beds (*'lectos pensiles'*) in which people could be rocked to reduce pain and induce sleep. Rocking was probably used as a sedative throughout the next centuries (Jütte, 2009), but only regained popularity with the construction of more sophisticated rotary chairs. In the beginning of the 19th century, Trommsdorf (1811) writes about the soothing effect of the rotary machines that were first recommended by Kratzenstein and, later, by Erasmus Darwin. Darwin thought that the rotatory movements would increase pressure on the patient's brain and therefore induce sleep (Wade, 2005). Joseph Mason Cox (1806) was probably the first to implement those ideas more systematically in clinical settings. While curing patients in an English institution known as the Fishpond asylum, Cox observed and described the soothing effect of his swing in patients with various disorders. Apart from vertigo, the treatment on the swing was followed by "the most refreshing slumbers" (Cox, 1806, p. 140), a characteristic which he considered highly valuable to cure his patients. Interestingly, subjective drowsiness is nowadays listed as a cardinal symptom of motion sickness as well as the so-called "sopite syndrome", a reaction in response to prolonged motion (Graybiel, 1969; Graybiel and Knepton, 1976; Guedry and Graybiel, 1961; Lawson and Mead, 1998), which matches Cox's observations of patients' becoming sleepy after having experienced his treatment. While investigating habituation to rotation, Dodge (1923a) reported that his participants described the experiment as having a "soothing and soporific character, both during and immediately after rotation" (Dodge, 1923a, p. 21). In the past 60 years, sleep researchers have developed an increasing interest in the effects of vestibular stimulation on sleep physiology and quality. As an example, the first manned space flights fueled the interest in the effects of a lack of gravity on sleep and motion sickness (e.g. Graybiel, 1969; Graybiel et al., 1968, 1960; Oosterveld et al., 1973).

A more recent study which focused on the intrinsic properties of sleep found that natural vestibular stimulation speeds up transition from wake to sleep and increases sleep stage N2 in daytime naps (Bayer et al., 2011). Vestibular stimulation was obtained using a bed that swung with a moderate to low frequency of 0.25 Hz and a peak horizontal acceleration of 0.1 m/s^2. Older studies have reported anecdotal but not statistical evidence for similar effects (Woodward et al., 1990). Bayer and colleagues (2011) argue that vestibular stimulation may enhance synchronicity in thalamo-cortical networks, caused by vestibular and somatosensory input to the thalamic nuclei, which could promote onset and maintenance of sleep. In a more therapeutic approach, Krystal and colleagues (2010) set out to investigate vestibular stimulation as a treatment of insomnia. They used GVS on normal sleepers with a model of transient insomnia, but found that it had an effect on sleep onset latency in only a specific subset of participants who had a sleep onset latency above the median ($\geq$ 14 minutes). In an experiment on herself, Vose (1981), previously a poor sleeper, describes deeper and longer sleep days after vestibular stimulation.

Vestibular stimulation seems to influence not only sleep characteristics but also properties of dreams (Leslie and Ogilvie, 1996). Indications about a connection arise from patients with vestibular disorders reporting strong vestibular imagery while dreaming (Doneshka and Kehaiyov, 1978). Additionally, in the aforementioned study by Woodward and colleagues (1990), participants claimed to have experienced intense dreams of a sexual nature after a night of vestibular stimulation. In this study, increased REM sleep density was measured. Longer and denser REM bursts after vestibular stimulation have also been found in children (Ornitz et al., 1973). On a side note, lucid dreaming is apparently more pronounced in young children (Voss et al., 2012). Interestingly, the frequency of lucid dreams seems to be related to the vestibular activity in sleep (Gackenbach et al., 1986). In a similar vein, Leslie and Ogilvie (1996) showed that vestibular stimulation lead to changes in dream mentation, including increased bizarreness and vestibular imagery. They hypothesized that activity of vestibular nuclei may contribute to lucid dreaming. Lucid dreaming is a promising treatment in various psychiatric conditions such as depression or post traumatic stress disorder, but induction of lucid dreaming is not always successful (Voss et al., 2014). Based on those findings, we speculate that vestibular stimulation during REM sleep could be an interesting way to induce lucid dreams (Noreika et al., 2010).

2.2. Vestibular stimulation in mood, anxiety, mania and depression

Next to calming effects, vestibular stimulation has been proposed to induce more specific mood changes. Early on, starting in ancient Greece, commonalities between vestibular related symptoms such as vertigo or dizziness and anxiety were noticed (see e.g. Balaban and Jacob, 2001 for a historical perspective). Even Sigmund Freud (1962) listed ‘locomotor vertigo’, defined as illusory movement, as an important symptom in anxiety neurosis (‘Angstneurose’), a disorder described by him. During the 20th century, vestibular functions began to be objectively quantified by measuring the vestibulo-ocular reflex elicited by caloric, galvanic and natural stimulation (Balaban and Jacob, 2001). As a consequence, there was a first report about abnormal vestibular functioning in patients with anxiety neurosis (Hallpike et al., 1951). Interestingly, the unusual vestibular situation experienced in space was reported to result in emotional disturbances amongst other alterations (Guedry and Graybiel, 1961). Moreover, it was found that patients with a vestibular disorder have a higher risk of suffering from depression, panic and anxiety disorders (e.g. Eagger et al., 1992; Godemann et al., 2004).

Strikingly, and besides the long known relationship between affective disorders and vestibular disturbances, there are only few records of attempts to use vestibular stimulation as a therapeutic tool in anxiety or related disorders. From the analysis of Cox's (1806) case reports it seems that he also treated patients with anxiety disorders on his swing, even if it is difficult to determine a clear psychopathological diagnosis based on his descriptions. He and also Hallaran further mention the cure of mania with motion devices (Breathnach, 2010), but again there is reasonable doubt as to whether their definition of mania would transfer to modern diagnostic criteria. Kelly (1989) describes a therapeutic approach in which rotation and spinning were applied in various body positions to provide complete vestibular stimulation of the semi-circular canals in order to treat agoraphobia. In one reported case, this treatment improved quality of life profoundly. Moreover, there is one study in which vestibular stimulation was used to test the integrity of the vestibular system in patients with a major depression (Soza Ried and Aviles, 2007) and two case studies that used CVS in patients with mania (Dodson, 2004; Levine et al., 2012). Those showed that right hemispheric activation through left CVS alleviated manic symptom severity (Dodson, 2004; Levine et al., 2012) and increased (but non-significantly) bilateral frontal and central alpha EEG band activation (Levine et al., 2012). Inspired by the anecdotal knowledge of mood enhancing swinging and rocking, a study in patients with dementia found that the use of a glider swing improved mood and relaxation (Snyder et al., 2001).

The mood altering effects of vestibular stimulation have also been described in healthy participants and seem to depend strongly on the type of motion applied. Using a motion device, passive yaw rotation elicited more comfortable feelings; pitch rotations elicited more alert and energetic feelings, and roll rotation elicited less comfortable feelings. Passive heave translation evoked more alert, less relaxed and less comfortable feelings, and surge translation more alerting feelings (Winter et al., 2012). Based on those findings and inspired by Cox' chair (cp. chapter 1.1), Winter and colleagues (2013) set out to look more closely at the effects of yaw rotation on mood. But in contrast to their previous findings, yaw rotation diminished positive mood. No study tried to use such knowledge yet for more specific, hypothesis-driven stimulation in patients with mood disorders.

Next to inducing specific emotions, vestibular stimulation has been suggested to alter affect control. Preuss and colleagues (2014a) showed an improvement of affect control during right cold CVS when positive stimuli were presented and an increased positive mood rating, while positive mood decreased during left cold stimulation. In a similar vein, left cold CVS was shown to reduce the desirability of a product (Preuss et al., 2014b) and to attenuate unrealistic optimism (McKay et al., 2013). Overall, activation of the right hemisphere through left cold CVS lowers the mood and vice versa. In conclusion, lateralized vestibular stimulation has been found to modulate mood in healthy participants, but clinical studies are scarce.

In a recent review, Coelho and Balaban (2014) hypothesize that visuo-vestibular conflicts are involved in a continuum of fear ranging from a lack of fear to panic attacks or exaggerated fear. Because in clinical practice fear-evoking visuo-vestibular cues are often neglected, they propose the construction of new visuo-vestibular expectations as a possible treatment. With technical progress and thus affordable head-mounted displays, virtual reality has become a valid alternative to in vivo exposure therapy in acrophobia (fear of heights) (for a review see Coelho and Balaban, 2014). They also hypothesize that a visuo-vestibular reconfiguration might be involved in the effectiveness of virtual reality therapy.

On a side note, we would like to point out that devices for vestibular stimulation are not only used in scientific and clinical settings but also for amusement. Hallaran noted, 200 years ago, that a few psychiatric patients used the motion device in the asylum for amusement (Breathnach, 2010). Today, they are an inherent part of playgrounds (swings, seesaw, rocking horses) and amusement parks (carousel, ferris wheel, roller coasters, graviton, tilt-a-whirl, drop tower). Interestingly, loud music with low frequencies, as played at rock concert or in clubs, has shown to activate the vestibular system. Based on this finding, listening to such loud music is hypothesized to be partly just another form of vestibular-mediated amusement seeking (Todd and Cody, 2000). Since bone-conducted vibration results in vestibular-evoked myogenic potentials and thus acts in a similar way on the vestibular system (e.g. Curthoys et al., 2014), it would be interesting to investigate the effect of bone-conducted vibration on mood.

2.3. Analgesic effects of vestibular stimulation

One thing that is sometimes mentioned together with the soothing effect of vestibular stimulation is its analgesic impact. Despite the early use of hanging beds to reduce pain (see above), the ‘spin doctors’ of the 19th century did not seem to apply their rotating chairs and moving beds primarily to alleviate pain. To our knowledge, renewed interest in the use of vestibular stimulation to alleviate pain is fairly recent. Kolev (1990) reports that cold CVS reduced the symptoms of pain during a migraine attack in 11 out of 12 participants. The success of the stimulation varied. In some participants the symptoms completely disappeared while others only noticed a slight decrease, and the duration of the effect varied, lasting from only a few minutes to several days.

Reduced pain after CVS has also been reported in amputees (André et al., 2001b) and paraplegics (Le Chapelain et al., 2001) with phantom limb pain - possibly mediated by a modification and normalization of the body schema by vestibular stimulation (see chapter 2.4. below). Further analgesic effects of CVS, which were still reported during follow-up several weeks later, were also found in two patients with central post-stroke pain (Ramachandran et al., 2007a, 2007b). These findings were replicated shortly thereafter; seven out of nine patients with central post-stroke pain reported decreased pain after CVS. The duration varied from only transient relief to several weeks (McGeoch et al., 2008). The analgesic effects were noticed mostly in the face and arms and less in the legs. The authors propose that this reflects the topographical map for pain in the posterior insula (Ramachandran et al., 2007a, 2007b). Alternatively, we speculate that it could reflect more generally the enlarged somatotopic representation of the face and arms on which CVS can act upon. Finally, these authors also successfully applied a similar CVS treatment in one patient with central post-stroke pain and tactile allodynia (McGeoch et al., 2009), as well as in a patient with unilateral central pain of spinal cord origin (McGeoch and Ramachandran, 2008).

Next to these effects of vestibular stimulation on chronic pain in patients, a recent experimental study in healthy participants found increased pain thresholds shortly after left cold CVS (Ferrè et al., 2013). It is not known, however, how long this effect lasts. Moreover, a study that investigated the effect of "simulated rocking" on the pain response to the so-called heelstick procedure in infants, found inconclusive results (Johnston et al., 1997), which could suggest that artificial stimulation is more likely to alleviate pain than natural vestibular stimulation due to its hemisphere specific (lateralized activation) nature.

While these analgesic effects of vestibular stimulation are potentially very important, more well controlled studies with adequate sample sizes are needed, and imaging or electrophysiological studies should be done in order to reveal the underlying mechanisms. An interaction between vestibular and nociceptive stimuli seems neurophysiologically plausible due to shared information processing (Balaban, 2011) particularly in the insula (zu Eulenburg et al., 2013) and/or the anterior cingulate cortex (McGeoch et al., 2009; Miller and Ngo, 2007); see Lenggenhager and Lopez (in press) and Mast and colleagues (2014) for a more thorough discussion of underlying physiological mechanisms. Furthermore, Ramachandran and colleagues (2007a) provide an interesting evolutionary and functional speculation on the link between pain and the vestibular system, in which they propose that activating the vestibular system is often a useful strategy to escape pain, which makes an interaction between the two systems plausible. Moreover, an interaction between pain and the vestibular system could generally be mediated by changes in the awareness of the bodily self, as hypothesized in a recent review (Lenggenhager and Lopez, in press; see also next chapter).

2.4. Vestibular stimulation in neurological body disorders of the bodily self and space

From the beginning of the 20th century on – especially with the early work of Bonnier (1905, 1893) and later with the one of Lhermitte (1939) and Schilder (1935), a strong link between the vestibular system and the experience of the space, the body and the self has been suggested. For example, Bonnier (1905) described various body perception alterations in patients with vertigo. Such a link between the vestibular system and the sense of an embodied self was later confirmed and strengthened by various findings showing, for example, body misperception in patients with peripheral vestibular disturbances as well as in healthy participants during artificial vestibular stimulation (Jauregui-Renaud et al., 2008; Sang et al., 2006; see also Lopez, 2013 for a review). These patients describe feelings like being separated from the body, not being in control of their own body and changes in the size of body parts. Such symptoms overlap with the experiences of patients with psychiatric or neurologically-caused disorders of the perception of the body, the self and space (see e.g. de Vignemont, 2010 for a comprehensive list of clinical syndromes). These disorders are traditionally related to right parietal dysfunctions (e.g. Critchley, 1953, 1950), although similar experiences have been described with lesions in other brain areas (e.g. Lopez et al., 2010a).

With the relatively early recognition of the importance of vestibular signaling in the representation of body and space, the use of vestibular stimulation to treat various disorders of the bodily self has increased slowly but steadily during the 20th century. In fact, Bonnier noticed already 1893 that the bodily illusions he observed in vestibular patients transiently decreased during vestibular stimulation (i.e. head shaking) (Bonnier, 1893). In 1941, Silberpfennig describes two patients with 'pseudohemianopic' disorder, i.e. a problem of drawing attention to the contralesional space, which was clearly attenuated during CVS (Silberpfennig, 1941). Since then the use of vestibular stimulation to increase spatial functioning in hemineglect has gained importance, and while early studies report short-term effects during single applications (e.g. Cappa et al., 1987; Rubens, 1985), more recent studies suggest that long-term effects can be induced using multiple sessions of artificial vestibular stimulation (Wilkinson et al., 2014). Alongside successful application of vestibular stimulation to normalize space awareness (see e.g. Chokron et al., 2007 for a review and a list of relevant studies), artificial vestibular stimulation has been used and suggested to be used as a therapeutic measure for patients with various bodily disorders. It has successfully been used to alleviate somatosensory hemi-inattention (Bottini et al., 2005; Schmidt et al., 2013), motor neglect (Vallar et al., 2003), anosognosia and personal neglect (Cappa et al., 1987), somatoparaphrenia (Rode et al., 1992), macrosomatognosia (Rode et al., 2012) as well as phantom limb sensation and pain (André et al., 2001a; Le Chapelain et al., 2001). Next to these positive (albeit not well-controlled findings), vestibular techniques have been enthusiastically propagated to treat a variety of other bodily disorders of both, neurological or psychiatric origin (Ramachandran et al., 2007a, 2007b; Ramachandran and McGeoch, 2007).

While most of these studies lack an explicit functional hypothesis, the effects are commonly ascribed to an activation of a higher-level, multisensory body representation by vestibular stimulation, which presumably restores the body representations and triggers a more accurate body perception through unification of multisensory input. Vestibular stimulation has been shown to activate predominantly retroinsular and temporo-parietal areas (e.g. Lopez et al., 2010b), areas that have generally shown to be important in multisensory and higher-level body and space representation (Blanke, 2012; Pfeiffer et al., 2014 for reviews). Importantly, almost all of these studies are single case studies, many do not include any sham stimulation (see e.g. Schmidt et al., 2013 for an exception) and have other methodological flaws. Furthermore, the effectiveness of the method might be overestimated due to publication bias (see Mast et al., 2014 for a brief discussion). For example, recent empirical evidence in a group of patients with a complex body disorder did not show any normalization during or after artificial vestibular stimulation (Lenggenhager et al., 2014). It remains to be seen whether other stimulation paradigms and types such as prolonged noisy GVS, used quite successfully in neurodegenerative patients so far (see chapter 2.8.), could increase effectiveness compared to traditional stimulations in certain psychiatric or neurological disorders such as body integrity identity disorder.

2.5. The use of vestibular stimulation to treat conversion disorders

Conversion disorders cover a range of symptoms such as blindness or deafness, paralysis, numbness, motor deficits, and other neurological symptoms that cannot be fully explained by physiological findings. Historically, the term ‘hysteria’ was used until Freud progressively introduced the term ‘conversion’, which refers to his theory that psychological symptoms are *converted* into physical symptoms (Bogousslavsky, 2011). Ernst Horn (1818; see also Harsch, 2006) described the use of his rotating bed (and chair) to treat hysteria with considerable success. However, Horn’s apparatus was particularly unpleasant as it applied substantial g-force and the fear of repeated spinning was considered as therapeutically valuable (Harsch, 2006). Hundred years later, just shortly after Bárány published his book on caloric stimulation (1907), Abercrombie and McKenzie (1910) suggested that CVS might be a useful diagnostic tool to differentiate between hysterical and organic deafness. McKenzie (1912) reports that he therefore applied CVS in a woman who had been deaf in her right ear since childhood and recently started to show signs of hysterical deafness in her left ear. Curiously, after the procedure, the woman was able to hear well again on her left side, while the impairment on the right remained unchanged. McKenzie (1912, p. 19) states the following reasoning regarding the positive effect: “The patient then volunteered the information that she had several times lost her voice, and had had it restored “by the battery.” And there can be no doubt that it was the memory of this previous successful treatment, coupled with the profound mental shock of the violent vestibular stimulation, which cured her deafness on this occasion.” Another hundred years later, Noll-Hussong and colleagues (2014) reported a case study of a young man with conversion disorder showing involuntary movements of the upper body. Left cold CVS of varying duration was applied three times. According to the patient’s report, the stimulation helped to attenuate the involuntary movements. Remarkably, after the third stimulation, these beneficial effects were still noticed three days later. Those authors assume that CVS - due to its cortical hemispheric lateralization - activates (and deactivates) critical brain areas (especially temporo-parietal areas, the anterior cingulate cortex, and insula) that drive the effects (compare also Lopez and Blanke, 2011).

2.6. Vestibular stimulation in schizophrenia

Surprisingly, schizophrenia emerged as a specific disorder relatively late in psychiatric history. Only in the late 19th hundred did Emil Kraepelin define ‘dementia praecox’ more closely, and shortly thereafter, in the early 20th century, Eugen Bleuler introduced the term ‘schizophrenia’. Before this introduction, schizophrenic symptoms may have been classed under more general concepts like ‘madness’ or even just ‘insanity’ (Bürgy, 2008; Heinrichs, 2003). This makes it difficult to trace the use of therapeutic vestibular stimulation in patients with schizophrenia through time. However, a few case reports and mental states have been described that possibly allude to schizophrenia as we know it today. Cox (1806), for example, describes some case studies (e.g. cases XVI, XVII and XX) that might be diagnosed as schizophrenia today. Another physician during Cox’s era, Horn (1818; see also Harsch, 2006), reports using the rotating bed during acute episodes of ‘raving madness’. But again, given the changing understanding of terms and definitions, interpretations are difficult.

Since the 1920’s, vestibular dysfunctions have been repeatedly observed in children and adults

with schizophrenia, especially abnormal eye movement responses; yet, some studies also failed to find significant differences compared to a control group (for an overview see e.g. Hixson and Mathews, 1984; Kelly, 1989; Levy et al., 1983). With the onset of Anna Jean Ayres's postulation of the sensory integration theory (e.g. Ayres and Heskett, 1972), which she started developing in the 1950's, sensory stimulation became the focus of different therapy interventions. Vestibular stimulation was typically an integral part in sensory integration therapies. Since the work of Schilder (1933), the vestibular system had been considered to help organize other sensory information and to have direct influences on both emotion, through the limbic system, and the experience of a coherent unified self. Furthermore, together with tactile and proprioceptive input, these ontogenetically earlier sensory systems were the focus because sensory integration aimed at promoting sequential development. However, because sensory integration therapy - as the name suggests - applies other sensory stimulation (typically tactile and proprioceptive) and also the vestibular stimulation often involves passive (e.g. swinging in a hammock) as well as active (e.g. riding a scooterboard) components (Ayres and Heskett, 1972), further elaboration is beyond the scope of this review (see instead Hixson and Mathews (1984) and Kelly (1989) for a review on the use of vestibular stimulation in this context).
Only recently, CVS was applied in two patients with schizophrenia (Levine et al., 2012). Interestingly, the results show transiently decreased delusions and decreased lack of insight-judgment as measured with the Positive and Negative Symptoms Scale after left cold CVS but not after right cold CVS (see also chapter 2.2.). Moreover, vestibular stimulation has been suggested to help improving the motor symptoms of catatonia (Miller and Ngo, 2007, see also chapter 2.8) and it may also help to improve cognitive functions (see chapter 2.9.). It should, however, be noted that administering vestibular stimulation may be counter-indicative, at least during an acute phase, among other concerns, because visual hallucinations have been reported after CVS in healthy participants (Kolev, 1995) and overstimulation could exacerbate the symptoms. Generally, again, the underlying mechanisms by which vestibular stimulation should improve symptoms of schizophrenia is not well understood and vestibular and even multisensory stimulation remain negligible in the treatment of schizophrenia.

2.7. Vestibular stimulation in neurodevelopmental disorders

Following Alexander Crum Brown's suggestion (1878), William James (1881) conducted early experiments with deaf children who "were whirled in a rotary swing" (p. 412). He observed that they were often less prone to motion sickness compared to hearing children. Despite these early (and questionable) scientific investigations in children and the fact that children often seek the pleasure of movement (e.g. playgrounds are full of vestibular stimulation devices, see also chapter 2.2.) vestibular treatment of children seemed (luckily) less 'fashionable' than for adults in the first half of the 19th century.

This changed in the second half of the 20th century, during which vestibular processes have increasingly been suggested to play an important role in a broad variety of developmental disorders (see e.g. Kelly, 1989 for an impressive list of disorders with presumable vestibular deficits) including dyslexia (Frank and Levinson, 1973), attention deficit hyperactivity disorder (ADHD) (Bhatara et al., 1978), autism (Ritvo et al., 1969), as well as more general learning deficits (Ayres and Heskett, 1972). Interestingly, some of their core symptoms have shown to be present in patients with vertigo (e.g. dyscalculia Risey and Briner, 1990; Smith, 2012 for a discussion), suggesting a mutual interaction between these symptoms and vestibular signaling. As a consequence, vestibular stimulation - at the time mostly delivered by motion devices - was increasingly used to treat children. While such approaches are interesting in the context of this paper and will therefore be reviewed briefly below, it is important to note that within the huge research field on neurodevelopmental disorders, they play a rather minor role.

In *dyslexia*, parallels have been drawn between various symptoms associated with developmental dyslexia (e.g. problems with postural stability, spatial orientation and eye movements) and the vestibular system, leading to the so-called cerebellar-vestibular dysfunction hypothesis of dyslexia (e.g. Levinson, 1988). Early therapies included treatment with anti-motion sickness medication (Levinson, 1991) as well as specific motion stimulation (e.g. Silver, 1986) and combined multisensory integration therapies (Ayres, 1978). Yet, these findings were already at that time heavily debated and even considered wrong (see Pope and Whiteley, 2003; Silver, 1986 for reviews), and have largely lost their influence on current models of dyslexia.

Similarly, *ADHD* is often associated with poor balance control and postural coordination, suggesting a vestibular and cerebellar contribution (e.g. Sergeant et al., 2006). Such interaction might be mediated by vestibular contributions to the parasympathetic and sympathetic systems (see Clark et al., 2008 for a extensive explanation). Corroboratively, several studies found a positive effect on attention disorder during vestibular stimulation treatment using motion devices (e.g. Arnold et al., 1985; Bhatara et al., 1981, 1978). However, a recent well-controlled study with a relatively large sample of patients concluded that these results were probably due to nonspecific effects, such as experimenter expectancy or attention given to the child, as they found improvement both in the experimental (rotation on a chair) and the control condition (sitting on the chair watching a video and hearing the same noise) (Clark et al., 2008).

About at the same time, a vestibular dysfunction theory was also proposed for *autism*, after data showed altered nystagmus response (Ornitz, 1970; Ritvo et al., 1969) as well as altered REM sleep in people with autism, and after vestibular stimulation was found to affect REM (Ornitz EM et al., 1973; see also chapter 2.1.). Most important in the context of this review, repeated rotatory stimulation has shown to improve motor skills of young autistic infants (Kantner et al., 1976).

2.8. Vestibular stimulation in neurodegenerative disorders

A relatively early, uncontrolled study reported that rotatory vestibular stimulation improved initiation of movement and a better posture in patients with Parkinson's disease (McNiven, 1986). However, Kelly (1989) also mentions unpublished work of Young (1987) that provides empirical support for the therapeutic success of vestibular stimulation in Parkinson's measured by an increase in step length.

Recent attempts have used GVS, since it includes activation of the vestibular nerve, which innervates autonomic and limbic-to-motor functions, and the regulation of dopamine and noradrenaline in those areas (Albert et al., 1985; Anderson et al., 2002). GVS was therefore hypothesized as possible treatment in neurodegenerative diseases targeting those areas like Parkinson's Disease and multiple system atrophy (Yamamoto et al., 2005). However, because constant GVS causes unilateral oculomotor and postural responses (Fitzpatrick and Day, 2004) and would therefore limit the benefit of such a stimulation, stochastic/noisy GVS was used in all studies on neurodegenerative disorders that we know of (Pal et al., 2009; Pan et al., 2008; Yamamoto et al., 2005). In their pioneering study, Yamoto and colleagues (2005) found that noisy GVS alleviated autonomic and motoric disturbances in Parkinson's Disease and multi system atrophy, and that it decreased reaction time in an attention and response control task but did not modulate cognitive performance. Moreover, stochastic GVS was found to stabilize small sway in Parkinson's Disease (Pal et al., 2009). In conclusion, the underlying mechanisms are still largely unknown (Kim et al., 2013).

2.9. Cognitive enhancement through vestibular stimulation?

There is now accumulating evidence that impaired or absent vestibular input (e.g. vestibular deficits, during weightlessness, or complete vestibular loss) can negatively affect cognitive functioning and has even found to result in hippocampus atrophy (for a review see e.g. Smith and Zheng, 2013). The question might therefore be if, conversely, additional vestibular stimulation can improve such functions. Here we briefly discuss studies that suggest that vestibular stimulation, beyond its therapeutic effects, might serve as a sensory and cognitive enhancer in healthy participants (Wilkinson et al., 2008). Besides the above reviewed positive effects of vestibular stimulation on various disorders, vestibular stimulation has shown to enhance both *sensory* (e.g. Ferrè et al., 2013) and *cognitive* (e.g. Falconer and Mast, 2012) *functions*. Especially, memory - visual memory recall (Wilkinson et al., 2008), and depending on stimulation side, verbal or spatial recall (Bachtold et al., 2001) - was found to be improved (for a review see Smith et al., 2010). Similarly, a recent EEG study suggested improved memory as well as altered frontal beta power after GVS (Lee et al., 2014). Given the positive effect of arousal on memory retention (e.g. Sharot and Phelps, 2004), one could speculate that such results might be explained by arousal caused by vestibular stimulation (Horowitz et al., 2005, see also chapter 2.1). To further investigate this interesting question on the influence of vestibular-induced arousal, one could use different strengths of vestibular stimulation to see whether the positive effect on memory depends on stimulation parameters. Furthermore stochastic galvanic stimulation has been shown to alter modulation of synchrony patterns in the EEG across a broad range of oscillations (i.e. frequency bands), possibly due to stochastic facilitation/resonance (Kim et al., 2013). Such biologically relevant noise may enhance neural information processing and computational goals (McDonnell and Ward, 2011).

Besides these positive effects on perceptual and cognitive processes, vestibular stimulation has been shown to decrease pain (Ferrè et al., 2013, see chapter 2.3) and - depending on the side of stimulation - improve affect control (Preuss et al., 2014a), alter mood (Winter et al., 2012) and decrease unrealistic optimism (McKay et al., 2013, see chapter 2.2). Moreover, there are some hints that vestibular stimulation has positive effects on sleep characteristics (see chapter 2.1.). All these outcomes are also linked to cognitive functioning, and cognitive enhancement after vestibular stimulation could be mediated by these positive effects on various states. Yet, it will probably play a minor role in the future compared to other neurocognitive enhancers, such as tDCS, that directly modulate cortical activation. Furthermore, most studies have not looked at long-term effects, and long-lasting improvements are unexplored.

3. Discussion

The aim of this review was to recapitulate the therapeutic use of vestibular stimulation. We introduced the origins and developments of the three main methods to passively stimulate the vestibular system (i.e. motion devices, CVS and GVS) and presented a selection of topics from psychiatric and neurological research, in which it is suggested that vestibular stimulation may be beneficial. We critically reassessed history, success and effectiveness of vestibular stimulation. Although this literature review covers a broad range of applications, it is by far not complete. Disorders that we have not discussed, but which we would like to mention here in order to provide a better appreciation of how widely vestibular stimulation has been applied, include also: pusher behavior (Krewer et al., 2013; Nakamura et al., 2014), aphasic syndrome (Wilkinson et al., 2013), prosopagnosia (Wilkinson et al., 2005) and figure-copying deficit after right hemispheric stroke (Wilkinson et al., 2010), intellectual disability (Dave, 1992) and Down's syndrome (e.g. Brocklehurst-Woods, 1990). Moreover, we only briefly mention the effects of vestibular stimulation on hemispatial neglect, albeit this is probably one of the most promising and thus already most discussed (Schmidt et al., 2013; Utz et al., 2010; Wilkinson et al., 2014) research branch of this field.

3.1. Methodological and ethical considerations of vestibular stimulation

The advantages and the resulting popularity of vestibular stimulation as a therapy are evident: it is usually non-invasive, rather cheap and easily applicable. Yet, while most of the studies reviewed here report a positive effect of vestibular stimulation (which might partly be due to publication bias), many of them need to be regarded with caution as they are often associated with methodological problems and their results might be heavily confounded by other effects. Furthermore, even if generally non-invasive, there are still counter indications of therapeutic vestibular stimulation. Already in the early 19th century it was for example not recommended to use vestibular stimulation in fragile, fearful, paranoid or hypochondriac patients nor in patients with organic disease (e.g. Horn, 1818). It was further only recommended in hopeless cases (Cox, 1806) or if no other less stressful methods could be used (Harsch, 2006), which has to be seen in the context of other medical treatments of that time. A contemporary view is important, as some of the former procedures would nowadays be regarded as torture. Such procedures were typically performed without the participant's consent and in the case of vestibular stimulation purposefully intense and nauseating. In fact, during the first half of the 19th century, the peak period of therapeutically applied motion devices, it was deliberately intended to induce motion sickness, vertigo, nausea and vomiting. The latter was a desired method for treatment during this time, along with others, such as, purging, bleeding, bathing, blistering, and the use of sedatives and stimulants (Cox, 1806; Harsch, 2006; Wade, 2005). Therefore, what is now viewed as the undesired side effects of vestibular stimulation were at the time actually intended. With the change of perspective on psychiatric patients and the call for more ethical treatments introduced by Philippe Pinel at the end of the 18th century and the resulting growth of his followers in the 19th century, the use of such

methods decreased, including the use of motion devices (Jütte, 2009).
Today, measures are taken to minimize those undesired effects. For example, the proposed intensity of real motion stimulation is now usually a calming rocking instead of vertiginous swinging and efforts are made to investigate and apply GVS at a sub-sensory threshold with remarkable results (Wilkinson et al., 2010). But even above threshold, if GVS is applied with caution, there are mild side effects and these are of transient nature (Utz et al., 2011). Moreover, repeated treatment sessions may be needed for a satisfying outcome and the safety seems to be warranted when using "low-intensity" (1 mA) GVS (Wilkinson et al., 2009). Yet, even if vestibular treatments today are much more humane, it should be noted that depending on stimulation parameters vestibular stimulation (especially artificial) might still induce considerable side effects (e.g. Lenggenhager et al., 2008). Independent of the side effects, it is important that the methods are carefully evaluated before suggesting vestibular stimulation as a therapy 'for everything' (e.g. see chapter 2.7.). Placebo effects as well as co-stimulation of other sensory systems (e.g. touch, pain) need to be considered as explanatory models and protocols should be hypothesis-driven rather than based on trial and error (Kelly, 1989). In addition, there are non-specific effects like stress (e.g. stress-induced analgesia, see Ossenkopp et al., 1988) which might influence the results. Importantly, such effects might not occur in a linear way. Low to modest intensity stimulation might for example lead to decreased stress-immune responses while high intensity may lead to increased stress-immune response compared to no stimulation. Moreover, the duration and repetition of the stimulation needs to be taken into account. In fact, talking about 'vestibular stimulation' as it is often done in the present review is an oversimplification, because the vestibular system is a complex system and its responsivity can change depending on the stimulation parameters and the targeted organs (otoliths and/or semicircular canals). Importantly, GVS can be applied by varying intensity, pulse profile and duration, and modern motion devices allow to deliver vestibular stimulation in a similarly precise fashion while CVS does not have these characteristics (Palla and Lenggenhager, 2014). A clear, detailed and ideally a priori defined and hypothesis-driven protocol and selection of the method to stimulate the vestibular organ is thus indispensable. In this context it is interesting to note that historically there seems to have been a tendency to use 'natural' vestibular stimulation through the use of motion devices to treat psychiatric disorders and artificial vestibular stimulation (CVS, GVS) to treat neurological disorders – a distinction which seems not justified by any functional or physiological hypothesis.
Furthermore, studies need to show that the effect of 'vestibular stimulation' is indeed due to the vestibular activation and not due to any co-activation of other sensory systems (e.g. touch, proprioception) or other unspecific effects. This is among the reasons why this review article focuses

on passive vestibular stimulation as opposed to active vestibular stimulation (e.g. slack-lining or rocking in a rocking chair), which may be beneficial due to other and difficult-to-control effects, especially motor activation. We also did not mention optokinetic stimulation, which has often proven useful in similar therapeutic approaches (e.g. Kerkhoff et al., 2006), but Is not a genuine vestibular stimulation.

3.2. What neurophysiological mechanisms can explain the effect of vestibular stimulation?

While this review contains a list of beneficial effects of vestibular stimulation on various conditions and disturbances, the reasons for such effects are still far from understood. Explicit explanation of underlying mechanisms of the positive effect is often lacking, and if present, the mechanism might just target a very specific effect of the vestibular stimulation. In fact, different core mechanisms have been proposed to explain potential therapeutic effects of vestibular stimulation, most prominently probably a) relocation of attention, b) multisensory integration, c) hemisphere specific activation, d) neurotransmitter release.

Relocation of attention, could be induced both by the directional nystagmus (for a discussion see Figliozzi et al., 2005) or by activation of attentional networks overlapping with brain areas targeted by vestibular stimulation (Oppenländer et al., 2014). This mechanism has particularly been put forward to help explain the positive effects on neglect and similar symptoms (see e.g. Karnath and Dieterich, 2006; Wilkinson et al., 2014). Such an attention shift could be caused by an unspecfic activation of parieto-temporal cortical areas contralateral to the stimulated ear. However, an attention shift due to CVS does not seem to always occur in healthy participants (e.g. Rorden et al., 2001). Recently, Ferrè and colleagues (2014) showed that the effect of vestibular stimulation on somatosensory detection was modulated by multimodal interaction rather than spatial attention. *The integration and activation of multisensory processing* areas (e.g. insula, parietal operculum, anterior cingulate cortex) by vestibular stimulation has been proposed to be the underlying factor in disorders of the bodily self (e.g. Bottini et al., 2013). The vestibular system is intrinsically multisensory because of its neuroanatomical connections and a vestibular percept is thus rarely experienced purely (Angelaki et al., 2009; Blanke, 2012; Ferrè et al., 2012). Moreover, it has been hypothesized that the vestibular system and emotional circuits overlap (Preuss et al., 2014a) or that CVS would target the inferior frontal gyrus, a region involved in unrealistic optimism (McKay et al., 2013). On an lower level, the medial vestibular nucleus located in the medulla oblongata is connected to different brain areas associated with nociception, sleep and arousal, homeostasis and eye movements (Horowitz et al., 2005). It remains to be seen how those structural connections translate to a more functional level. The *hemispheric specific activation*/deactivation pattern has been suggested to enhance or hinder specific lateralized brain processes (McKay et al., 2013; Noll-Hussong et al., 2014; Preuss et al., 2014b) . On a smaller scale, vestibular stimulation influences *neurotransmitter release* (for a discussion see Gurvich et al., 2013; Mast et al., 2014). The alteration of specific neurotransmitters such as dopamine, serotonin and GABA are thus crucial for understanding the influence of vestibular stimulation on cognition. For example GVS increases GABA release in rats (Samoudi et al., 2012). But also the sleep-wake system is influenced by vestibular input as projections of the medial vestibular nucleus to hypocretin neurons and vice versa have been found (Horowitz et al., 2005).

Of course, such explanatory models act on differently scaled levels and are not mutually exclusive but may represent different aspects of a shared underlying mechanism.

Finally, as already pointed out, non-specific effects like stress, general arousal, or placebo effects need also to be considered.

The question remains whether there is a more general/common mechanism underlying all these effects and if so, which would be the most promising. Yet, given the broad spectrum of disorders targeted with different underlying dysfunctions, pursuing a ‘one-size-fits-all’ approach might be too ambitious.

3.3. Outlook

This literature review shows that vestibular stimulation has been, and still is, a popular method and certainly contributed to the understanding and treatment of certain disorders. However, since most studies discussed in this review are case or small-scale studies, and often never replicated, an overestimation of its efficiency due to publication bias needs to be considered. This is especially important, because publication bias mostly affects exactly such studies, while sufficiently powered studies are usually published disregarding the actual outcome (Egger et al., 1997; Thornton and Lee, 2000). Therefore, large-scale studies including clinical trials and/or randomized control trials are needed. Such studies are feasible since vestibular stimulation is readily available, inexpensive and many of the discussed disorders, like sleep disorders, chronic pain, depression and anxiety, are unfortunately very prevalent.

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